A Dissertation on

"A PROSPECTIVE STUDY TO COMPARE THE EFFICACY OF RECOMBINANT EPIDERMAL GROWTH FACTOR IN WOUND HEALING WITH NORMAL SALINE DRESSING"

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with partial fulfillment of the regulations

for the Award of the degree

M.S. (General Surgery)

Branch – I

MADRAS MEDICAL COLLEGE,

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APRIL-2017

BONAFIDE CERTIFICATE

Certified that this dissertation is the bonafide work of **Dr. FELIX CORDELIA.M.J,** on **"A PROSPECTIVE STUDY TO COMPARE THE EFFICACY OF RECOMBINANT EPIDERMAL GROWTH FACTOR IN WOUND HEALING WITH NORMAL SALINE DRESSING "** during her M.S. (General Surgery) course from March 2016 to September 2016 at the Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 600003.

Prof. Dr. P.RAGUMANI. M.S.
Director,
Institute of General Surgery,
Madras Medical College &
Rajiv Gandhi Government
General Hospital,
Chennai - 600 003.

Prof. Dr. K.RAMASUBRAMANIAN, M.S.,
Professor of General Surgery,
Institute of General Surgery,
Madras Medical College &
Rajiv Gandhi Government
General Hospital,
Chennai - 600 003.

Prof. Dr. M. K. MURALIDHARAN M.S., M.Ch,
DEAN,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai – 600 003.

DECLARATION

I hereby solemnly declare that the dissertation titled, "**A PROSPECTIVE STUDY TO COMPARE THE EFFICACY OF RECOMBINANT EPIDERMAL GROWTH FACTOR IN WOUND HEALING WITH NORMAL SALINE DRESSING"**, is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2015-16 under the guidance and supervision of **Prof.Dr.K.RAMASUBRAMANIAN,M.S.,** The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai towards the partial fulfillment of requirements for the award of M.S. Degree (Branch-I) in General Surgery.

Date

Place:

Dr. FELIX CORDELIA.M.J
Post Graduate student,
M.S. General Surgery
Institute of General Surgery,
Madras Medical College,
Chennai-3.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

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Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.M.J.Felix Cordelia
Post Graduate in M.S. General Surgery
Madras Medical College & RGGGH
Chennai 600 003

Dear Dr.M.J.Felix Cordelia,

The Institutional Ethics Committee has considered your request and approved your study titled **"PROSPECTIVE STUDY TO COMPARE THE EFFECTS OF HUMAN RECOMBINANT EPIDERMAL GROWTH FACTOR IN WOUND HEALING WITH NORMAL SALINE DRESSING"- NO. 05042016.**

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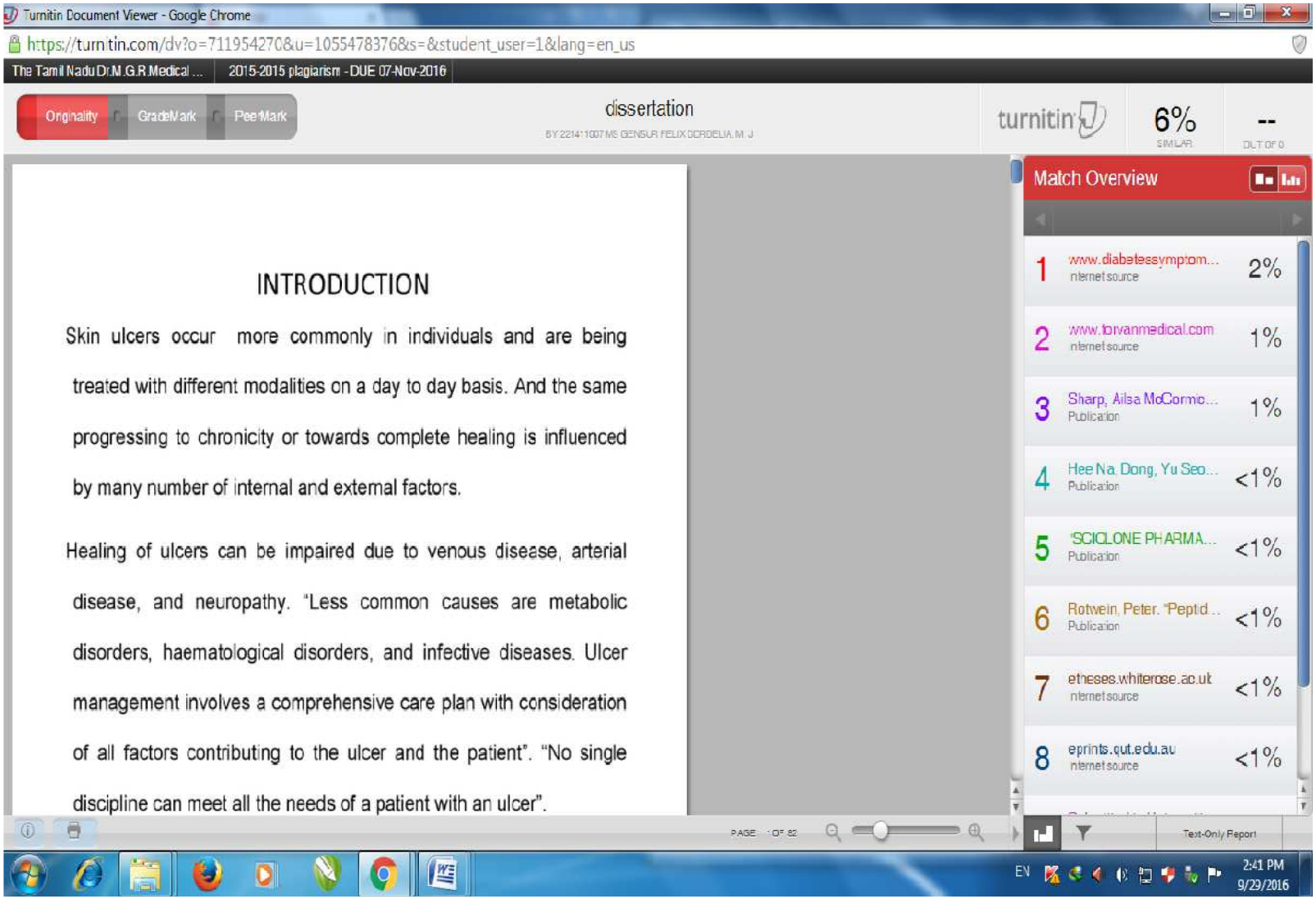
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Skin ulcers occur more commonly in individuals and are being treated with different modalities on a day to day basis. And the same progressing to chronicity or towards complete healing is influenced by many number of internal and external factors.
Healing of ulcers can be impaired due to venous disease, arterial disease, and neuropathy. "Less common causes are metabolic disorders, haematological disorders, and infective diseases. Ulcer management involves a comprehensive care plan with consideration of all factors contributing to the ulcer and the patient". "No single discipline can meet all the needs of a patient with an ulcer".
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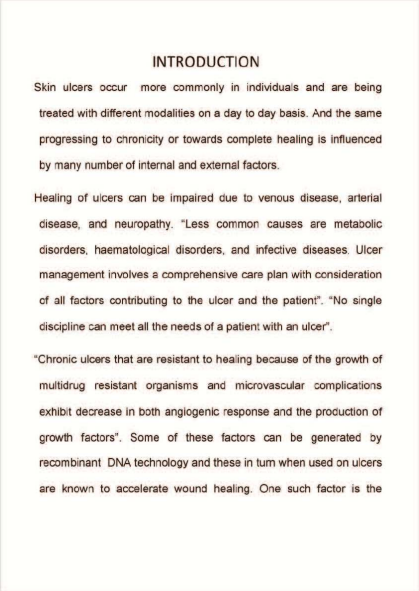

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"Chronic ulcers that are resistant to healing because of the growth of multidrug resistant organisms and microvascular complications exhibit decrease in both angiogenic response and the production of growth factors". Some of these factors can be generated by recombinant DNA technology and these in turn when used on ulcers are known to accelerate wound healing. One such factor is the

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I would like to express my deep sense of gratitude to **Prof. Dr. M. K. MURALIDHARAN M.S., M.Ch,** the **DEAN**, Madras Medical College and **Prof. Dr. P.RAGUMANI M.S**, Director, Institute of General Surgery, MMC & RGGGH, for allowing me to undertake this study on **"A PROSPECTIVE STUDY TO COMPARE THE EFFICACY OF RECOMBINANT EPIDERMAL GROWTH FACTOR IN WOUND HEALING TO NORMAL SALINE DRESSING"**

I was able to carry out my study to my fullest satisfaction, thanks to the guidance, encouragement, motivation and constant supervision extended to me, by my beloved Unit Chief **Prof. Dr. K. RAMASUBRAMANIAN M.S**. Hence my profuse thanks are due for him.

I am bound by ties of gratitude to my respected Assistant Professors**, Dr. S.Umarani, Dr. S.VijayaLakshmi, Dr. Sendhil Kumar, Dr.Anandi,** in general, for placing and guiding me on the right track from the very beginning of my career in Surgery till this day. I would be failing in my duty if I don't place on record my sincere thanks to those patients who inspite of their sufferings extended their fullest co-operation.

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Lastly, my lovable thanks to my parents, husband and daughter for their moral support.

Dr. FELIX CORDELIA.M.J

CONTENTS

LIST OF TABLES

ABBREVIATIONS

EGF	Epidermal Growth Factor
PDGF	Platelet Derived Growth Factor
rhEGF	Recombinant Human Epidermal Growth Factor
DM	Diabetes Mellitus
HTN	Hypertension
CAD	Coronary Artery Disease
NS	Normal saline
CKD	Chronic Kidney Disease
SLE	Systemic Lupus Erythematosis

ABSTRACT

BACKGROUND AND OBJECTIVE

Ulcers are a cause of morbid illness prolonging the hospital stay of patients for want of utmost care in order to avoid amputations. Various advanced treatment modalities are being available these days to reduce the morbidity and quicken the process of healing

One such readily available product is the Human Recombinant Epidermal Growth Factor which has proven efficacy in increasing the healing rate. This study is aimed at comparing the efficacy of rhEGF (available in the brand name REGEN D 150) to normal saline dressings in improving the healing rate of large ulcers .

METHODS

Between March 2016 and September 2016, 104 patients with ulcers who got admitted to Institute of General Surgery, Rajiv Gandhi Government General Hospital, Chennai were recruited to the study by randomising them to test and control groups. The study ended with 100 patients , 50 in each group and both the systems were compared. The effects of rhEGF on wound healing were analysed and compared to that of the conventional normal saline dressing.

RESULTS

The study group dressed with rhEGF showed a significant reduction in size of the ulcers irrespective of other comorbidities or sites of ulcer. The healing rate was calculated as percentage reduction in size per week and the significance was analysed. Further analysis was done on the infectivity rate of ulcers in each group and found that rhEGF significantly prevents ulcers from micro organism colonisation.

INTERPRETATION AND CONCLUSION

The efficacy of rhEGF in ulcer healing as analysed in many studies was found to be higher than the usual conventional normal saline dressing and this effect was statistically significant. Large ulcers treated with rhEGF showed an increased healing rate and ulcer was made ready for skin grafting sooner than usual thus avoiding unnecessary amputations.

KEY WORDS

ulcers, wound healing, growth factors, rhEGF, normal saline, wound dressing, diabetes, infection, antibiotics

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Healing of ulcers can be impaired due to venous disease, arterial disease, and neuropathy. “Less common causes are metabolic disorders, haematological disorders, and infective diseases. Ulcer management involves a comprehensive care plan with consideration of all factors contributing to the ulcer and the patient”. “No single discipline can meet all the needs of a patient with an ulcer”.

“Chronic ulcers that are resistant to healing because of the growth of multidrug resistant organisms and microvascular complications exhibit decrease in both angiogenic response and the production of growth factors”. Some of these factors can be generated by recombinant DNA technology and these in turn when used on ulcers are known to accelerate wound healing. One such factor is the recombinant Human Epidermal Growth Factor which helps in the stimulation of cell growth resulting in faster wound healing.

“The recombinant human EGF is a single chain polypeptide with 54 amino acids. It is identical to that of human natural EGF composed of 53 amino acids”.

AIM OF STUDY

AIM OF STUDY

- TO COMPARE THE EFFICACY OF RECOMBINANT HUMAN EPIDERMAL GROWTH FACTOR WITH THAT OF NORMAL SALINE DRESSING IN ULCER HEALING.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

"From the era of living in caves, men have been tending to their wounds. Wound care has evolved from incantations, potions, and local applications to a systematic text of wound care and surgery from Hippocrates and Celcius".

"The Middle Ages regressed back to charms and potions and this continued till the time of great wars when wound care emerged again".

"In history, this was followed by the realisation of the necessity of hygiene and the halting of bleeding, where wound dressing and surgical skills developed. Eventually the germ theory of disease also assisted in improving wound care'.

The first advances in wound care began in 19th century with the work of Ignaz Philip Semmelweis, a Hungerian obstetrician who developed sterile surgical procedures and Louis Pasteur, a French scientist known as the Father of Microbiology for his germ theory.

WOUND DRESSING: PAST TO PRESENT

"With advancements in materials and tissue science, the field of wound dressings has evolved considerably. The ability to bolster wound re-epithelialization has been improved. The advent of numerous synthetic products in the field of wound care have significantly accelerated the

process of natural wound healing". Semmelweis's work was furthered by an English surgeon, Joseph Lister, who began treating his surgical gauze with carbolic acid, known today as phenol, and subsequently dropped his surgical team's mortality rate by 45%. Building on the success of Lister's pretreated surgical gauze, Robert Wood Johnson co-founder of Johnson & Johnson began producing gauze and wound dressing treated with Iodine.

These innovations in wound-site dressings marked the first major steps forward in the field since the advances of the Egyptians and Greeks, centuries earlier.

The next advances would arise from the development of polymer synthetics for wound dressings and the "rediscovery" of moist wound-site care protocols.

THE PROCESS OF WOUND HEALING

"The process by which tissue repair takes place is termed wound healing and is comprised of a continuous sequence of inflammation and repair, in which epithelial, endothelial, inflammatory cells, platelets and fibroblasts briefly come together outside their normal domains, interact to restore a semblance of their usual discipline and having done so resume their normal function".

“The process of wound repair differs little from one kind of tissue to another and is generally independent of the form of injury. Although the different elements of the wound healing process occur in a continuous, integrated manner, it is convenient to divide the overall process into three overlapping phases and several natural components for descriptive purposes”.

Inflammatory Phase:(Day 0-5)

Coagulation

“The healing response is initiated at the moment of injury. Surgical or traumatic wounds disrupt the tissue architecture and cause haemorrhage. Initially, blood fills the wound defect and exposure of this blood to collagen in the wound leads to platelet degranulation and activation of Hageman factor. This in turn sets into motion a number of biological amplification systems including the complement kinin and clotting cascades and plasmin generation. These serve to amplify the original injury signal and lead not only to clot formation, which unites the wound edges, but also to the accumulation of a number of mitogens and chemoattractants at the site of wounding”.

Inflammation

“Production of both kinins and prostaglandins leads to vasodilatation and increased small vessel permeability in the region of the wound . This results in oedema in the area of the injury and is responsible for the pain and swelling which occurs early after injury. Within 6 h, circulating immune cells start to appear in the wound. Polymorphonuclear leucocytes (PMN) are the first blood leucocytes to enter the wound site. They initially appear in the wound shortly after injury and subsequently their numbers increase steadily, peaking at 24-48 h . Their main function appears to be phagocytosis of the bacteria which have been introduced into the wound during injury. The presence of PMN in the wound following injury does not appear to be essential in order for normal wound healing to take place , with healing proceeding normally in their absence provided that bacterial contamination has not occurred. In the absence of infection, PMN have a relatively short life span in the wound and their numbers decrease rapidly after the third day” .

“The next cellular, immune element to enter the wound are macrophages. These cells are derived from circulating monocytes by a combination of migration and chemotaxis. They first appear within 48-96 h post-injury and reach a peak around the third day post-injury. These macrophages have a much longer life span than the PMN and persist in

the wound until healing is complete. Their appearance is followed somewhat later by T lymphocytes, which appear in significant numbers around the fifth day post-injury, with peak numbers occurring about the seventh day after injury. In contrast to PMN, the presence and activation of both macrophages and lymphocytes in the wound is critical to the progress of the normal healing process".

"Macrophages just like neutrophils phagocytose and digest pathological organisms and tissue debris. In addition, macrophages release a plethora of biologically active substances. Many of these substances facilitate the recruitment of additional inflammatory cells and aid the macrophage in tissue decontamination and debridement; in addition growth factors and other substances are also released which are necessary for the initiation and propagation of granulation tissue formation. These intercellular transmitters are known collectively as cytokines".

Proliferative Phase: (Day 3-14)

"In the absence of significant infection or contamination the inflammatory phase is short, and after the wound has been successfully cleared of devitalized and unwanted material it gives way to the proliferative phase of healing. The proliferative phase is characterized by the formation of granulation tissue in the wound".

Fibroplasia

“Granulation tissue consists of a combination of cellular elements, including fibroblasts and inflammatory cells, along with new capillaries embedded in a loose extra cellular matrix of collagen, fibronectin and hyaluronic acid. Fibroblasts first appear in significant numbers in the wound on the third day post-injury and achieve peak numbers around the seventh day. This rapid expansion in the fibroblast population at the wound site occurs via a combination of proliferation and migration. Fibroblasts are derived from local mesenchymal cells, particularly those associated with blood vessel adventitia, which are induced to proliferate and attracted into the wound by a combination of cytokines produced initially by platelets and subsequently by macrophages and lymphocytes. Fibroblasts are the primary synthetic element in the repair process and are responsible for production of the majority of structural proteins used during tissue reconstruction. In particular, fibroblasts produce large quantities of collagen, a family of triple-chain glycoproteins, which form the main constituent of the extracellular wound matrix and which are ultimately responsible for imparting tensile strength to the scar. Collagen is first detected in the wound around the third day post-injury, and thereafter the levels increase rapidly for approximately 3 weeks. It then continues to accumulate at a more gradual pace for up to 3 months post

wounding. The collagen is initially deposited in a seemingly haphazard fashion and these individual collagen fibrils are subsequently reorganised, by cross-linking, into regularly aligned bundles oriented along the lines of stress in the healing wound. Fibroblasts are also responsible for the production of other matrix constituents including fibronectin, hyaluronic acid and the glycosaminoglycans. The process of fibroblast proliferation and synthetic activity is known as fibroplasias".

Revascularization

"Revascularization of the wound proceeds in parallel with fibroplasia. Capillary buds sprout from blood vessels adjacent to the wound and extend into the wound space. On the second day post-injury, endothelial cells from the side of the venule closest to the wound begin to migrate in response to angiogenic stimuli. These capillary sprouts eventually branch at their tips and join to form capillary loops, through which blood begins to flow. New sprouts then extend from these loops to form a capillary plexus. The soluble factors responsible for angiogenesis remain incompletely defined. It appears that angiogenesis occurs by a combination of proliferation and migration. Putative mediators for endothelial cell growth and chemotaxis include cytokines produced by platelets, macrophages and lymphocytes in the wound, low oxygen tension, lactic acid and biogenic amines. Of the potential cytokine

mediators of neovascularization basic fibroblast growth factor (bFGF), acidic FGF (aFGF), transforming growth factors-a and b (TGF-a and -b) and epidermal growth factor (EGF) have all been shown to be potent stimuli for new vessel formation. FGF, in particular, has been shown to be a potent inducer of in vivo neovascularisation".

Re-epithelialization

"While these events are proceeding deep in the wound, restoration of epithelial integrity is taking place at the wound surface. Re-epithelialization of the wound begins within a couple of hours of the injury. Epithelial cells, arising from either the wound margins or residual dermal epithelial appendages within the wound bed, begin to migrate under the scab and over the underlying viable connective tissue. The epidermis immediately adjacent to the wound edge begins thickening within 24 h after injury. Marginal basal cells at the edge of the wound loose their firm attachment to the underlying dermis, enlarge and begin to migrate across the surface of the provisional matrix filling the wound. Fixed basal cells in a zone near the cut edge undergo a series of rapid mitotic divisions, and these cells appear to migrate by moving over one another in a leapfrog fashion until the defect is covered. Once the defect is bridged, the migrating epithelial cells loose their flattened appearance, become more columnar in shape and increase in mitotic activity. Layering

of the epithelium is re-established and the surface layer eventually keratinized. Reepithelialization is complete in less than 48 h in the case of approximated incised wounds, but may take substantially longer in the case of larger wounds where there is a significant tissue defect. If only the epithelium is damaged, such as occurs in split thickness skin graft donor sites, then repair consists primarily of re-epithelization with minimal or absent fibroplasia and granulation tissue formation. The stimuli for re-epithelization remain incompletely determined, but it appears that the process is mediated by a combination of loss of contact inhibition, exposure of constituents of the extracellular matrix, particularly fibronectin, and by cytokines produced by immune mononuclear cells. EGF, TGF-b, bFGF, platelet-derived growth factor (PDGF) and insulin like growth factor-l (IGF-l) in particular, have been shown to promote epithelialisation".

Maturation Phase: (Day 7 to I Year)

"Almost as soon as the extracellular matrix is laid down, its reorganization begins. Initially, the extracellular matrix is rich in fibronectin, which forms a provisional fibre network. This serves not only as a substratum for migration and ingrowth of cells, but also as a template for collagen deposition by fibroblasts. There are also significant quantities of hyaluronic acid and large molecular weight proteoglycans present,

which contribute to the gel-like consistency of the extracellular matrix and aid cellular infiltration. Collagen rapidly becomes the predominant constituent of the matrix. The initially randomly distributed collagen fibres become cross-linked and aggregated into fibrillar bundles, which gradually provide the healing tissue with increasing stiffness and tensile strength. After a 5-day lag period, which corresponds to early granulation tissue formation and a matrix largely composed of fibronectin and hyaluronic acid, there is a rapid increase in wound breaking strength due to collagen fibrogenesis. The subsequent rate of gain in wound tensile strength is slow, with the wound having gained only 20% of its final strength after 3 weeks. The final strength of the wound remains less than that of uninjured skin, with the maximum breaking strength of the scar reaching only 70% of that of the intact skin".

"This gradual gain in tensile strength is due not only to continuing collagen deposition, but also to collagen remodelling, with formation of larger collagen bundles and alteration of intermolecular crosslinking. Collagen remodelling during scar formation is dependent on both continued collagen synthesis and collagen catabolism. The degradation of wound collagen is controlled by a variety of collagenase enzymes, and the net increase in wound collagen is determined by the balance of these opposing mechanisms. The high rate of collagen synthesis within the

wound returns to normal tissue levels by 6-12 months, while active remodelling of the scar continues for up to 1 year after injury and indeed appears to continue at a very slow rate for life".

"As remodelling progresses, there is a gradual reduction in the cellularity and vascularity of the reparative tissue which results in the formation of a relatively avascular and acellular collagen scar. Grossly this can be observed as a reduction in erythema associated with the earlier scar and some reduction in the scar volume, resulting in a pale thin scar. This is normally a desirable feature of healing; however, in some cases shrinkage of the scar may give rise to an undesirable reduction in skin mobility resulting in contracture".

Wound contraction

"It involves the inward movement of the wound edge, is a further important element in the healing process and should be distinguished from contracture. Sharply incised wounds without significant tissue loss, approximated early after injury, heal rapidly without the need for significant reduction in the wound volume. Such wounds are described as having healed by primary intention. Large wounds, however, particularly those associated with significant tissue loss, heal by secondary intention, with granulation tissue gradually filling the defect and epithelization proceeding slowly from the wound edges. Contraction of the wound

edges can lead to a significant reduction in the quantity of granulation tissue required to fill the wound defect and a reduction in the area requiring reepithelization, with a consequent reduction in scar volume. Contraction is only undesirable where it leads to unacceptable tissue distortion and an unsatisfactory cosmetic result. Although contraction normally accounts for a larger part of overall wound closure in loose skinned animals, it still accounts for a significant proportion of the healing process in man, particularly in areas where the skin is not tightly bound down to underlying structures, such as on the back, neck and forearms. Initially following injury, where the wound edges are not approximated, there is a slight retraction of the wound edges due to the release of normal elastic tension in the skin, with a resultant increase in wound volume. The wound area starts to decrease rapidly from the third day onwards. While this is due in part to reepithelization, the main reason is an inward movement of the uninjured skin edges. Wound contraction usually begins around the fifth day postwounding and is complete by 12-15 days after wounding. Fibroblasts within the wound appear to be responsible for providing the force for this contractile activity. It was initially felt that specialized fibroblasts called myofibroblasts provided the motive force for wound contraction via a muscle like cell contraction. More recent studies reveal that wound contraction occurs as a result of an interaction between fibroblast locomotion and collagen reorganisation.

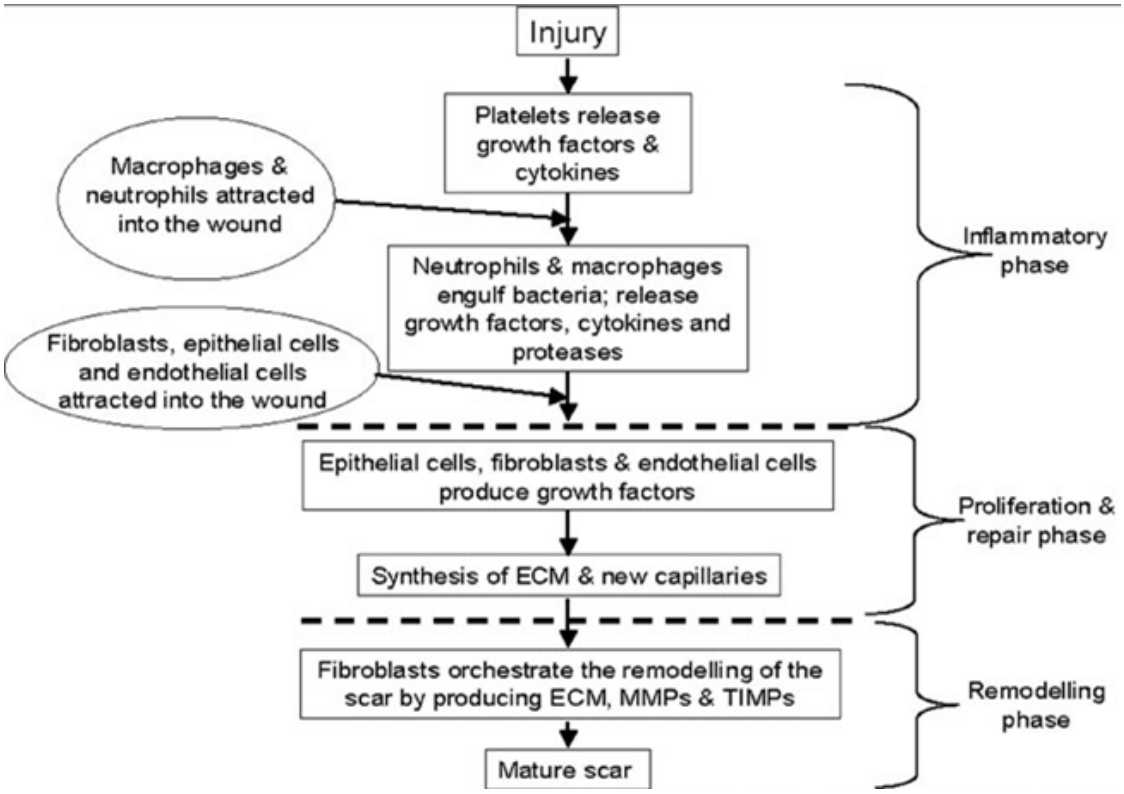
The contraction is thought to be mediated via the attachment of collagen fibrils to cell surface receptors, with the resulting tractional forces generated by cell motility bringing the attached collagen fibrils closer together and eventually compacting them".

"The regulation of wound contraction remains poorly defined. Information regarding the effects of specific cytokines on contraction is limited and often conflicting. TGF-b has been found to promote contraction even in the absence of serum"

Scar Formation

"As mentioned previously, the process of wound healing is essentially similar in all tissues and is relatively independent of the mode of injury; however, slight variation in the relative contribution of the different elements to the overall result may occur. The final product of the healing process is a scar. This relatively avascular and acellular mass of collagen serves to restore tissue continuity, strength and function. Delays in the healing process cause the prolonged presence of wounds, while abnormalities of the healing process may lead to abnormal scar formation. Successful completion of wound healing may not always yield the desired clinical result, particularly where the final cosmetic appearance of the scar is of primary importance".

WOUND HEALING- PROCESS



GROWTH FACTORS

"The understanding of concepts of growth factors in wound healing over the decade has brought new field of interest in their usage in chronic ulcers". Various studies conducted in vitro and clinical trials proved their efficacy in cell proliferation and angiogenesis and wound contraction.

"Recombinant technology made it possible to acquire adequate quantity of growth factors for human trials. Many such trials of growth factor use in wound healing were conducted. EGF is now approved for topical treatment of chronic and large wounds thereby preventing amputations to a certain extent".

“Growth factors are proteins secreted from many tissues in the body and exert varied effects on cell function. Growth factors stimulate or inhibit progression through the cell cycle that control cell viability or death, or that act principally to regulate cell differentiation”.

Their modes of action include

- autocrine,
- paracrine,
- juxtacrine,
- intracrine modes.

Autocrine actions are mediated by a growth factor on its cell of origin after its secretion into the extra cellular environment”. “Paracrine actions occur when a growth factor that is secreted by one cell has an effect on adjacent cells.

Juxtacrine is similar to paracrine except that the growth factor is bound to the cell membrane or extra cellular matrix.

Intracrine actions occur inside the cell of origin. The effects of growth factors are mediated by activation of specific receptors which are transmembrane proteins”.

Table 1 shows various growth factors involved in wound healing

Growth factor	Cell source	Principle action(s) in wound healing
EGF family		
EGF	Platelets	Stimulates proliferation of epithelial cells, fibroblasts and vascular endothelial cells
TGF-α	Platelets Macrophages Keratinocytes Eosinophils	Similar to EGF, more potent inducer of angiogenesis
Hb-EGF	Macrophages	Mitogenic for keratinocytes
Amphiregulin	Keratinocytes	Mitogenic for some cells, inhibits others. Role in wound healing not yet established
TGF-β family		
TGF-β_{1-3} (There are five subunits of TGF-β, however only TGF-β_{1-3} are found in mammalian cells)	Macrophages Lymphocytes Fibroblasts Keratinocytes Platelets	Inhibits proliferation of many cell types in vitro, including keratinocytes, endothelial cells and macrophages. May inhibit or stimulate fibroblasts.
PDGF family		
PDGF	Fibroblasts Vascular endothelial cells Vascular smooth muscle cells	Attracts fibroblasts, smooth muscle cells, monocytes and neutrophils into the wound
VEGF	Pituitary cells Macrophages Keratinocytes	Mitogen for vascular endothelial cells, stimulates angiogenesis
IGF family		
IGF- I	Fibroblasts Macrophages Platelets	May promote migration of endothelial cells into the wound. Mitogenic for fibroblasts.
FGF Family		
aFGF and bFGF (The IGF family includes IGF- I and IGF- II. IGF- I usually represents this family)	Macrophages Neural tissue Fibroblasts Astrocytes Endothelial cells Bone cells Smooth muscle	Mitogens for tissues of mesenchymal and neural origin
KGF	Fibroblasts	Mitogen for epithelial cells

EGF = epidermal growth factor; TGFα= transforming growth factor alpha; Hb-EGF = heparin binding epidermal growth factor; VEGF = vascular endothelial growth factor; TGFβ= transforming growth factor beta; IGF = insulin-like growth factor; PDGF = platelet derived growth factor; FGF = fibroblast growth factor; aFGF = acidic FGF; bFGF = basic FGF, KGF= keratinocyte growth factor

TISSUE MANAGEMENT/WOUND BED PREPARATION

A. DEBRIDEMENT

"Debridement of necrotic tissue is an integral component in the treatment of chronic wounds since they will not heal in the presence of unviable tissue, debris, or critical colonization. Undermined tissues or closed wound spaces would otherwise harbour bacterial growth. Debridement serves various functions: removal of necrotic tissue and callus; reduction of pressure; evaluation of the wound bed; evaluation of tracking and tunnelling; and reduction of bacterial burden. Debridement facilitates drainage and stimulates healing. However, debridement may be contraindicated in arterial ulcers. Additionally except in avascular cases, adequate debridement must always precede the application of topical wound healing agents, dressings, or wound closure procedures. Of the five types of debridement (surgical, enzymatic, autolytic, mechanical, biological), only surgical debridement has been proven to be efficacious in clinical trials".

(i) SURGICAL DEBRIDEMENT

"Surgical Debridement is the cornerstone of management of necrotising fasciitis and abscesses. Thorough sharp debridement of all nonviable soft tissue and bone from the open wound is accomplished with a scalpel, curettes, and curved scissors. Excision of necrotic tissue extends

as deeply and proximally as necessary until healthy, bleeding soft tissue and bone are encountered. Any callus tissue surrounding the ulcer must also be removed. The main purpose of surgical debridement is to turn an infected or necrotic soft tissue into an acute healing wound. Ulcers associated with a deep abscess requires hospital admission and immediate incision and drainage. Joined resection or partial amputation of the foot is necessary if osteomyelitis, joint infection, or gangrene is present. Necrotic tissue removed on a regular basis can expedite the rate at which a wound heals and has been shown to increase the popularity of attaining full secondary closure. Less frequent surgical debridement can reduce the rate at which a wound is healing and secondarily increase the risk of infection. Surgical debridement is repeated as often as needed if new necrotic tissue continues to form. Frequent debridement, referred to as maintenance debridement, is commonly required".

(ii) ENZYMATIC DEBRIDEMENT

"A highly selective method, enzymatic debridement consists of the application of exogenous proteolytic enzymes specifically manufactured for wound debridement. Various enzymes have been developed, including bacteria collagenase, plant derived papain / urea, fibrinolysin / DNAse, trypsin, streptokinase - streptodornase combination; only the first three products are widely available commercially. Collagenases are enzymes

that are isolated from *Clostridium histolyticum*. These specify high specificity for the major collagen types (I and II), but they are not active against keratin, fat, or fibrin. Papain, obtained from the papaya plant is effective in the breakdown of fibrinous material and necrotic tissue. When combined with urea, it denatures nonviable protein matter. The enzymatic compounds are inactivated by hydrogen peroxide, alcohol and heavy metals including silver, lead and mercury. One study found that wounds treated with papain-urea developed granulation tissue faster than those treated with collagenase".

(iii) MECHANICAL DEBRIDEMENT

"A nonselective, physical method of removing necrotic tissue, mechanical debridement may include wet-to-dry dressings and high-pressure irrigation or pulsed lavage and hydrotherapy. Wet-to-dry is one of the most commonly used and overused methods of debridement in acute care settings. Hydrotherapy in the form of whirlpool may remove surface skin, bacteria, wound exudates, and debris. There may be justification in the early stages of the wound for the use of this technique, but it is detrimental to friable granulation tissue".

B. BIOLOGICAL (MAGGOT) THERAPY

"Larval therapy utilizes the sterile form of the *Lucilia sericata* blowfly for the debridement of necrotic and infected wounds. Maggots

secrete a powerful proteolytic enzyme that liquefies necrotic tissue. It has been noted that wound odour and bacterial count, including methicillin-resistant *Staphylococcus Aureus*, diminish significantly with larval therapy. Larval therapy seems to be beneficial, but there is paucity of controlled studies to support its routine use in the diabetic foot wound".

C. MOISTURE BALANCE

"One of the major breakthroughs in wound management over the past 50 years was the demonstration that moisture accelerates re-epithelialization in a wound. Tissue moisture balance is a term used to convey the importance of keeping wounds moist and free of excess fluids. A moist wound environment promotes granulation and autolytic processes. Effective management of chronic wound fluids is an essential part of wound bed preparation; it also helps in addressing the issues of cellular dysfunction and biochemical imbalance".

D. DRESSINGS

"Wound dressings can be categorized as passive, active or interactive. Passive dressings primarily provide a protective function. Active and interactive dressings and therapies are capable of modifying a wound's physiology by stimulating cellular activity and growth factor release. An example is oxidized regenerated cellulose / collagen

(Promogran, Johnson & Johnson Inc., New Brunswick, NJ). Composed of collagen and oxidised regenerated cellulose, this bioabsorbable matrix decreases tissue destruction and prevents growth factor degradation. Recently silver has been added to this product (Prisma, Johnson & Johnson Inc., New Brunswick, NJ) to also provide an effective antibacterial buffer. Although these products are commonly used in clinical practice, they have not yet been conclusively shown to expedite wound healing".

Table 2 TIME principles of wound bed preparation

	Clinical finding	Action required
T	Tissue – necrotic, devitalized tissue	Debridement – removal of all devitalized tissue
I	Infection and/or inflammation	Removal of focus of infection or treatment of infection with topical/systemic agents
M	Moisture imbalance	Use of moisture-balancing dressings or negative pressure
E	Edge of wound – undermining or non advancement of wound edges	Reassess for devitalized tissue, infection, and moisture imbalance

WOUND CARE PRODUCTS

Table No 3A Shows Wound Care Products

A wide variety of wound care products are available; a brief listing of dressings and topical agents is presented in Table No 3A and 3B

Category	Indications	
Dressings		
Gauze Pad Sterile Gauze Sterile Cotton	Low to heavily draining wounds or surgical wounds Wet to dry debridement	Undefined
Transparent Films Polyurethane film with drainage adhesive layer, semi permeable	Dry to minimally draining wounds Promote tissue hydration	Infection Significant change Over prominence or friction
Hydrogels Gel, sheet, gauze (95% water or glycerin)	Dry to minimally draining wounds	Moderate or heavy drainage
Foam Polyurethane foam (open cell, absorbent)	Moderate, large exudate Clean wound surface Super absorbent and conformable to topography	Dry wounds
Hydrocolloids Water with adhesion, (carboxymethylcellulose pectin, gelatin) impermeable to oxygen	Low to moderate drainage Prevents tissue hydration	Heavy drainage Sinus tract

Calcium alginates Fiber pad derived from seaweed (may be combined with silver or collagen)	Heavy exudative wounds	Minimal drainage or dry wounds
Collagen dressings Particles or composite pads with collagen components (derived from bovine collagen)	Low to heavily raining wounds	Dry wounds
Antimicrobial dressings Contain silver, iodine in various forms preparations (eg, cadoxemer iodine)	Infected or clean wounds to prevent infection	Allergies to components

Table No 3B Shows Wound Care Products

Category	Indications	
Topical Therapies/Agents		
Amorphous Hydrogels **Skin Cleansers** Isotonic solutions for irrigation, hydrating dressings	Clean or infected wounds	Undefined
Detergents/Antiseptics Povidone-Iodine, Chlorhexidine Chloroxylenol Hypochlorite Benzethonium Chloride	Contaminated or infected wounds	Healthy granulating wounds
Topical Antibiotics Bacitracin, neomycin Mupirocin, polymyxin B Silver sulfadiazine Mafenide (creams, ointments)	Contaminated or infected wounds	Healthy granulating wounds
Enzymes Collagenase Papain-urea	Necrotic tissue Escharotic wounds	Healthy or infected wounds

ADVANCED WOUND CARE MODALITIES

"Wound bed preparation offers clinicians a comprehensive approach to removing barriers to healing and stimulating the healing process so that the benefits of advanced wound care can be maximized. Advanced care may sometimes be the only means of rapidly and effectively attaining wound closure. The advent of therapeutic growth factors, gene therapy, tissue-engineered constructs, stem cell therapy, and other drugs and devices that act through cellular and molecular-based mechanisms is enabling the modern surgeon and wound-care provider to actively promote wound angiogenesis to accelerate healing".

I) GROWTH FACTOR THEORY

"Chronic ulcers have demonstrated benefit from autologous platelet releasatesor genetic engineered products such as recombinant DNA platelet derived growth factor . This agent has been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts and monocytes and other monocytes that form the cellular basis of wound healing. In one pivotal randomized placebo-controlled blinded trial involving patient with full thickness diabetic foot ulcers, recombinant human platelet-derived growth factor (Becaplermin) demonstrated a 43% increase in completed closures vs placebo gel (50% vs 35%). Other growth factors, including

vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and keratinocyte growth factor (KGF), have been under study".

"Autologous platelet-rich plasma treatments utilize the patient's own blood to create a gel that is applied to the wound. Activation of the plasma after centrifugation stimulates the release of multiple growth factors from the platelet's alpha granules and the conversion of the plasma fibrinogen to a fibrin matrix scaffold. Both actions may assist with the new tissue formation. A large retrospective study reviewing this treatment protocol in commercial wound healing centers suggested a benefit in healing of larger and more severe neuropathic ulcer".

II) ADJUNCTIVE MODALITIES

i) **"Regenerative tissue matrix** is a new therapy used in diabetic foot ulcers, although it has undergone any random clinical trials to date. This allograft skin is minimally processed to remove the epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and visualization".

ii) **"Hyperbaric Oxygen therapy (HBO)** has shown promise in the treatment of diabetic foot wounds with hypoxia sever enough to interfere with the healing. However, most of the HB studies were hampered by methodological errors that preclude any definite role

for this modality in the routine treatment of diabetic foot ulcers. Nevertheless, in 2003, Medicare and Medicaid coverage for HBO extended to ulcers classified as Wagner grade 3 or higher that failed standard wound care therapy. Clearly, a large multicenter randomized clinical trial is needed to properly test the efficacy of this expensive modality"

iii) **"Several new ultrasound devices** are being used toboth debride the wound and provide ultrasonic theory. The MIST therapy system (Celleration, Eden Prairie, MN) is an ultrasonic device approved by the Food and Drug Administration (FDA) for wound debridement and cleansing. MIST Therapy uses a fine saline spray that allows ultrasound to be administered directly to the wound bed without contact to the affected tissue, thus minimizing the potential trauma to delicate capillary buds and emerging islands of epithelium".

iv) **"Negative pressure wound therapy (NPWT)**has become a common adjunctive treatment modality for diabetic foot ulcerations. Use of a vacuum-assisted closure device (V.A.C., KCI, San Antonio, TX) promotes wound healing through the application of topical, sub atmospheric, or negative pressure to the wound base. This therapy removes edema and chronic exudates, reduces bacterial colonization, enhances formation of new blood vessels, increases cellular proliferation, and improves wound oxygenation

as the result of applied mechanical force. These actions are synergistic. Numerous applications of this modality have proven successful, including use over exposed bone, tendons, and hardware to generate granulation tissue. It is also frequently used to facilitate adherence of split thickness skin grafts, rotational flaps, or tissue substitutes to a wound bed. A recent clinical trial of the V.A.C. device for the treatment of open amputation wounds in the diabetic foot showed significantly faster healing and development of granulation tissue with NPWT compared with standard moist wound care".

v) "The rationale for using **electrical simulation** in wound healing sterns from the fact that the human body has an endogenous bioelectric system that enhances healing of bone fractures and soft tissue wounds. Laboratory and clinical studies provide an abundance of support for the use of electrical simulation in wound care. In a randomized, controlled study evaluating wound healing using electrical simulation in neuropathic ulcers, significant differences in healed ulcer areas and number of healed ulcers at 12 weeks were found in the group receiving electrical stimulation compared with the control group".

III) PRESSURE RELIEF/OFF-LOADING

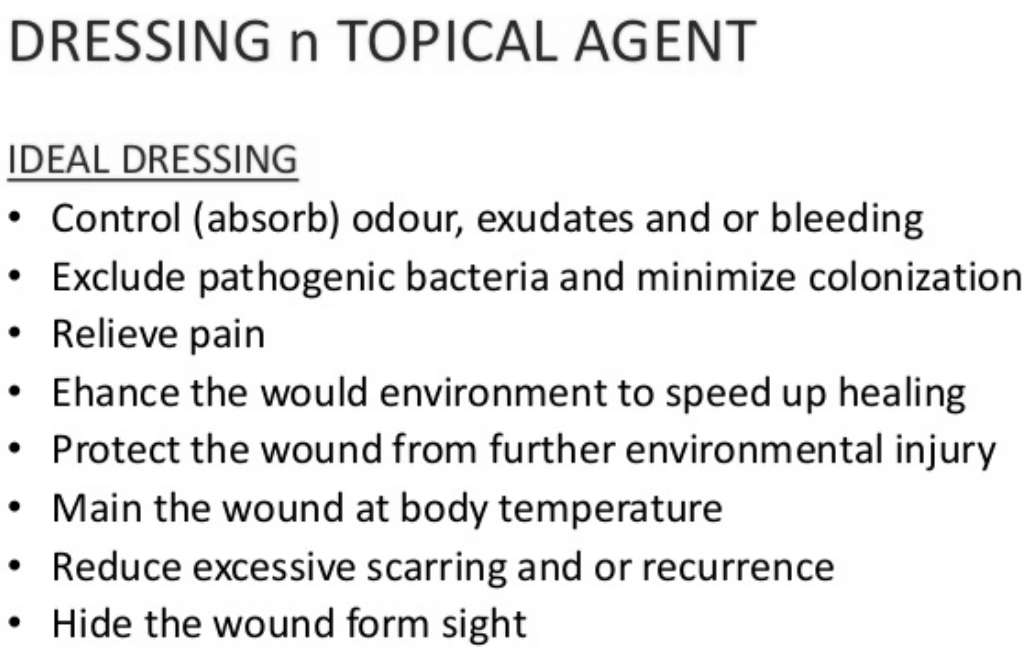
"The reduction of pressure especially to the diabetic foot ulcer is essential to treatment. Proper off-loading and pressure reduction prevents further trauma and promotes healing. This is particularly important in the diabetic with decreased or absent sensation in the lower extremities. Furthermore, recent studies provide evidence that minor trauma (eg, repetitive stress, shoe pressure) plays a major role in the casual pathway to ulceration".

"The choice of off-loading modality should be determined by the patient's physical characteristics and ability to comply with the treatment as well as by the location and severity of the ulcer. A study published in 2001 noted that the use of Total Contact Cast (TCC) heals better".

"The shoe causing ulcer should be removed till ulcer heals and to be replaced by new modified footwear".

IDEAL DRESSING

"Goal of wound dressing is to provide warm moist environments that are free of external contamination. The ideal dressing for granulation tissue should be one that is soft, absorbent, non-adherent and non-allergic. Although the ideal dressing does not exist, there are groups of dressing providing a comprehensive cure".



RECOMBINANT EPIDERMAL GROWTH FACTOR DRESSING

"REGEN D 150 contains indigenously developed recombinant Human Epidermal Growth factor (EGF) that helps in stimulation of cell growth resulting in faster wound healing".

EPIDERMAL GROWTH FACTOR

"EGFs are produced by several different cell types and act on epithelial cells, stimulating their migration and cell division. EGF has been shown to enhance wound healing. Besides growth factor , other extra cellular signals including disruption of cell-cell or cell matrix

contacts and the provisional matrix, might contribute to the initiation of migration reepithelialization and activation of gene expression".

"EGF is a polypeptide involved in the maturation of epithelial. It binds to the EGF receptor (EGFR) which is also a receptor for cytokines such as TGF-alpha. In normal adult epidermis, EGFR is predominantly expressed in basal keratinocytes and signalling events elicited by it are known to affect their proliferation, differentiation and migration. In healing skin wounds, EGFR expression is up regulated in migrating and proliferating keratinocytes adjacent to the wound. Clinical studies of the influence of treatment of skin wounds with soluble EGF have revealed a stimulatory function of this growth factor in wound healing. An early event after treatment of cultured epithelial cells with EGF is remodelling of the actin cytoskeleton, which can lead to retraction of cells from the substrate and rounding. EGF also stimulates centrifugal outwards migration of keratinocytes within colonies".

"Resident cell types, which comprise the skin, such as the keratinocytes and fibroblasts, have proved growth responsiveness to EGF in tissue culture. The necessary receptor, EGFR for binding of EGF and TGF-alpha is present in normal skin. Thus, wounded skin could respond to either endogenous or exogenous application of EGF. Published studies of other proliferative conditions indicate that EGF, TGF-alpha or the EGFR

is greatly increased in skin. Several in vitro and in vivo reports suggest that a proliferative process such as wound healing should be responsive to exogenous manipulation using EGF”.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design	:	Prospective randomised control trial
Source of data	:	Patients admitted to various surgical units at the Institute of General Surgery, Madras Medical College, Chennai were the source of sample
Study period	:	March 2016 – September 2016
Sample size	:	Totally 104 patients were enrolled in the study
Control group	:	52 patients
Study group	:	52 patients

Wherein 1 patient in the study group and 1 patient in the control group lost follow up. 1 patient in the control group had to undergo amputation and 1 patient in the study group had limb ischemia.

Hence the study was concluded with 100 patients , 25 in each group.

Inclusion Criteria :

a) All patients above 18 yrs of age
b) Traumatic, infectious, venous or pressure ulcers
c) Grade I or II ulcers defined by Wagner's classification on any part of the body
d) Ulcers with adequate perfusion

e) Patients presenting with necrotising fasciitis or abscesses or bedsores were enrolled in the study after initial debridement of the affected area

Exclusion criteria :

a) Below 18 yrs

b) Pregnant women

c) All ischemic ulcers with Doppler proven occlusion of vessels

d) Radiologically proven osteomyelitis

e) All malignant ulcers

f) Electrical or radiation wounds

g) Burns wounds

Methods :

- Patients with above mentioned criteria admitted to our hospital were included in the study.
- Proforma was attached to their case records and filled up with details necessary before the start of the study.
- After a thorough clinical examination, they were investigated. Besides the routine haematological and biochemical parameters, USG Doppler for vascular evaluation and x-ray of the affected part were done to look for any evidence of osteomyelitis and were excluded from the study

- Good glycemic control was ensured by diabetic diet and adjusting the dose of insulin with periodic blood sugar measurements.
- After initial thorough debridement the dressings were started and subsequent debridements were done as and when required
- The patients were randomised into two groups of 27 each.
- The size of the ulcer was measured by cutting a gauze piece to the size of the wound and calculating the surface area of the ulcer approximately.
- Wound swab was taken for culture and sensitivity in all cases and antibiotics were given wherever necessary as per the sensitivity pattern
- The study group were dressed with recombinant epidermal growth factor gel and the other group were dressed with routine normal saline dressing.
- All the wounds were measured once in two weeks and the value recorded in the proforma.
- The final measurement was done at the end of 6 weeks and an endpoint wound swab culture done.
- The difference between the initial and final measurement was taken into account for analysis of results.

Table 4 WAGNER'S CLASSIFICATION

Grade	Lesion
0	No open lesions: may have deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer to tendon or joint capsule
3	Deep ulcer with abscess, osteomyelitis, or joint sepis
4	Local gangrene - forefoot or heel
5	Gangrene of entire foot

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER

CONTROL GROUP

2 WEEKS

4 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

2 WEEKS

6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

ON ADMISSION

6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

ON ADMISSION

6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

ON ADMISSION

6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

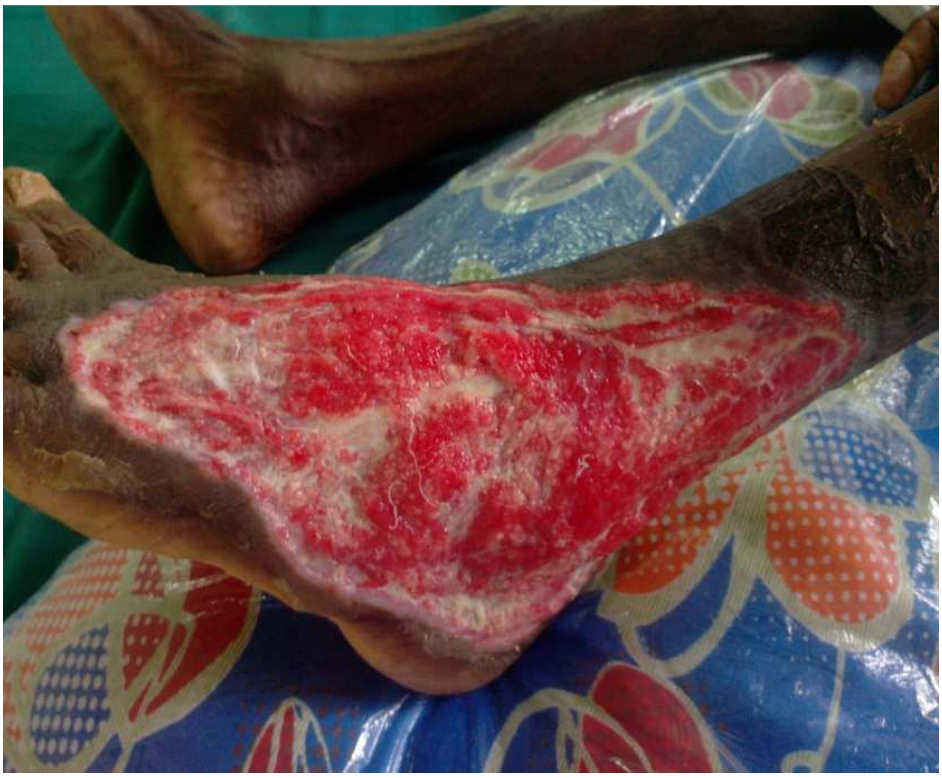
2 WEEKS

4 WEEKS

PICTURE SHOWING SMALLEST ULCER SIZE

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER

CONTROL GROUP



AT 6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER

CONTROL GROUP

2 WEEKS

6 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

ON ADMISSION

2 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

TRAUMATIC FOREARM ULCER

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

ON ADMISSION

4 WEEKS

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

SCROTAL ULCER

PICTURE SHOWING WOUND HEALING IN A PATIENT UNDER STUDY GROUP

2 WEEKS

6 WEEKS

RESULTS

RESULTS

Sample size : Total of 104 patients were recruited to the studyTwo patients one from each group lost follow up and were excluded.

One patient in control group had to undergo amputation as he developed uncontrolled sepsis.

One patient in study group had doppler confirmed ischemia and was excluded.

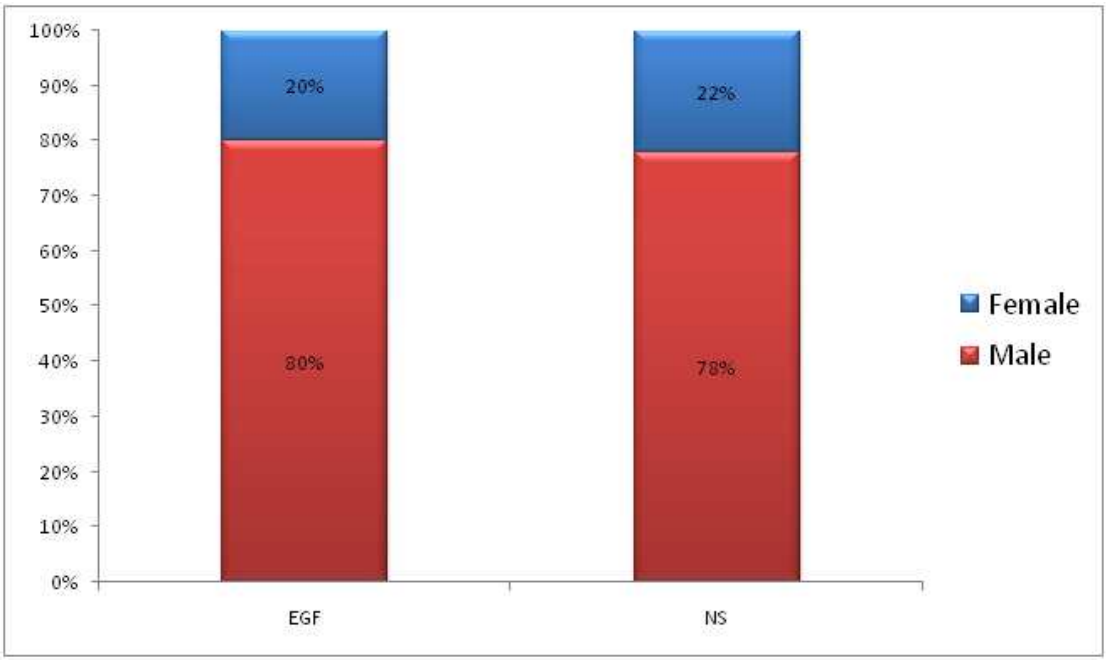
The study ended with 100 patients with

Study group having 50 patients and

Control group having 50 patients.

SAMPLE SIZE DISTRIBUTION

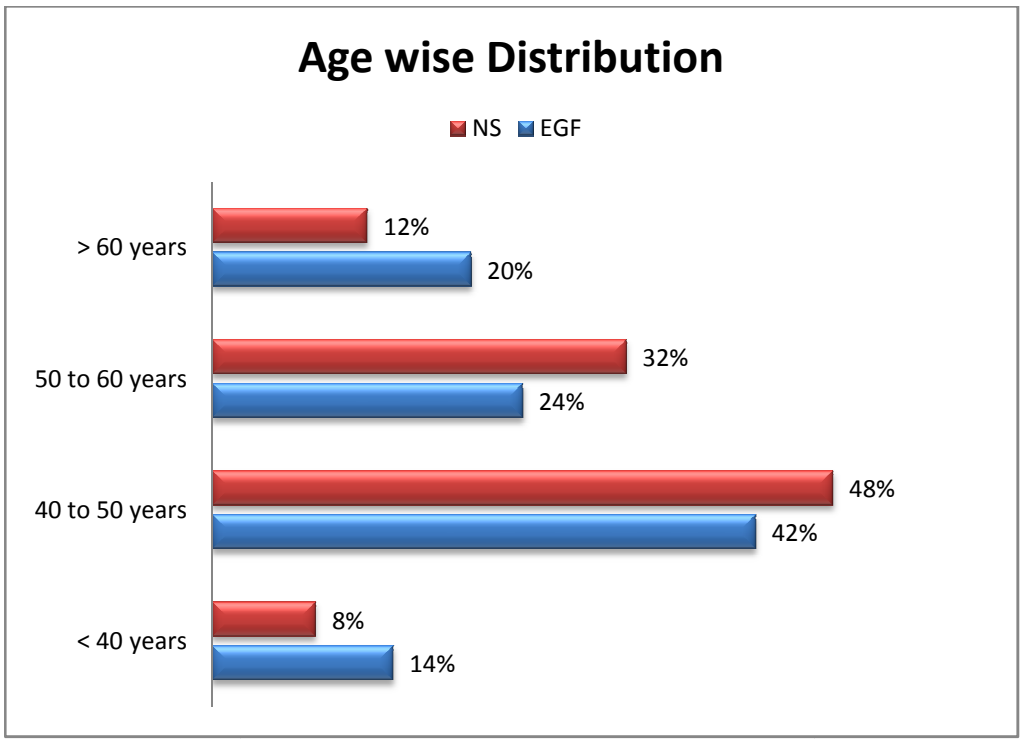
Gender distribution :



Category	Female	Male	Total
EGF	10	40	50
NS	11	39	50
Total	**21**	**79**	**100**

The gender distribution in both groups were predominantly males and the percentage was similar in both groups.

AGE WISE DISTRIBUTION

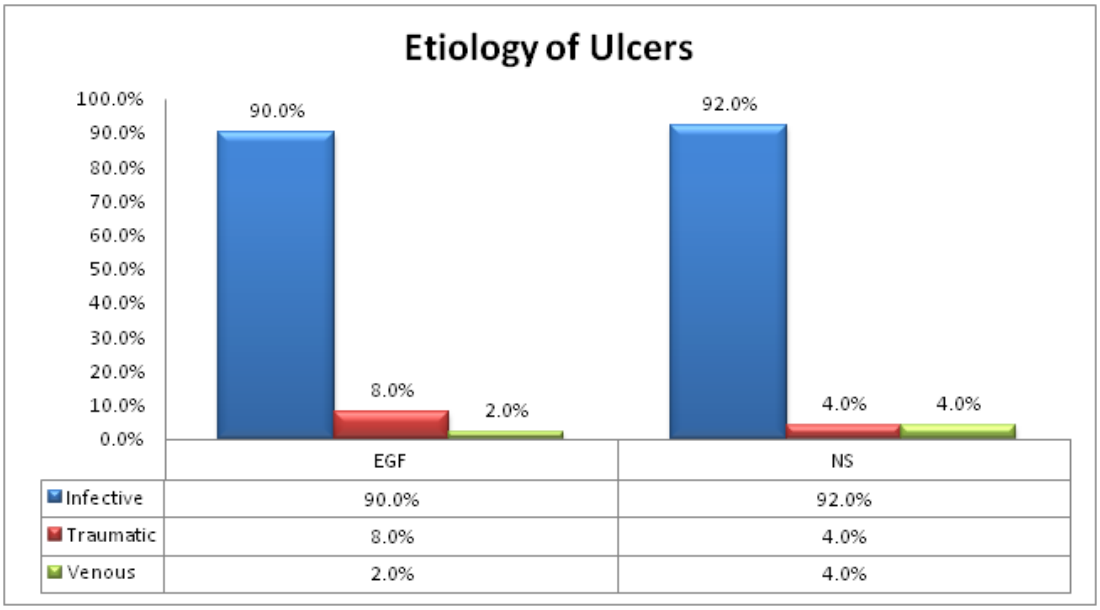


Category	< 40 years	40 to 50 years	50 to 60 years	> 60 years	Total
EGF	7	21	12	10	50
NS	4	24	16	6	50
Total	**11**	**45**	**28**	**16**	**100**

Most of the patients in our study were between 40 and 50 yrs which was similar in both groups.

The youngest patient was 28 yrs old and the eldest was 71 Years. Mean age was 51.1 years overall,(SD)

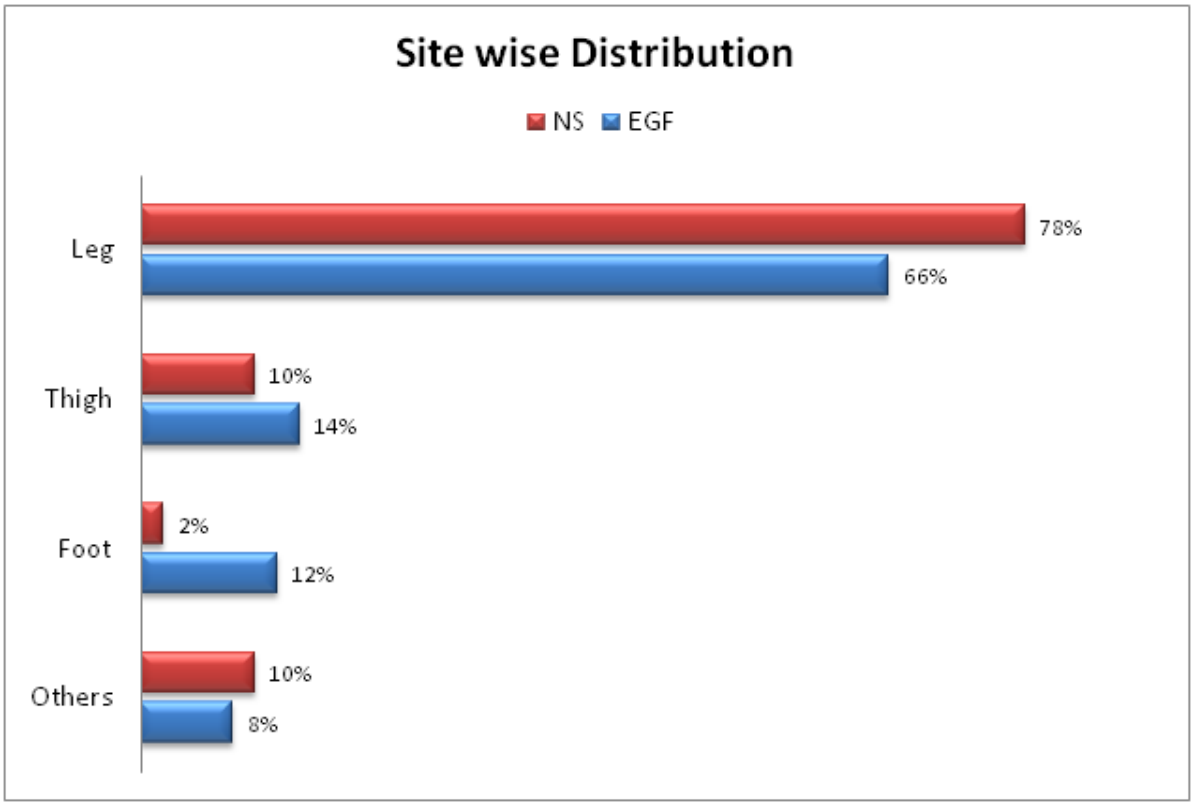
ETIOLOGY OF ULCERS



Category	Infective	Traumatic	Venous	Total
EGF	45	4	1	50
NS	46	2	2	50
Total	**91**	**6**	**3**	**100**

The most common etiology was infective and found to be similar in both groups. The second most common cause was traumatic followed by venous ulcers.

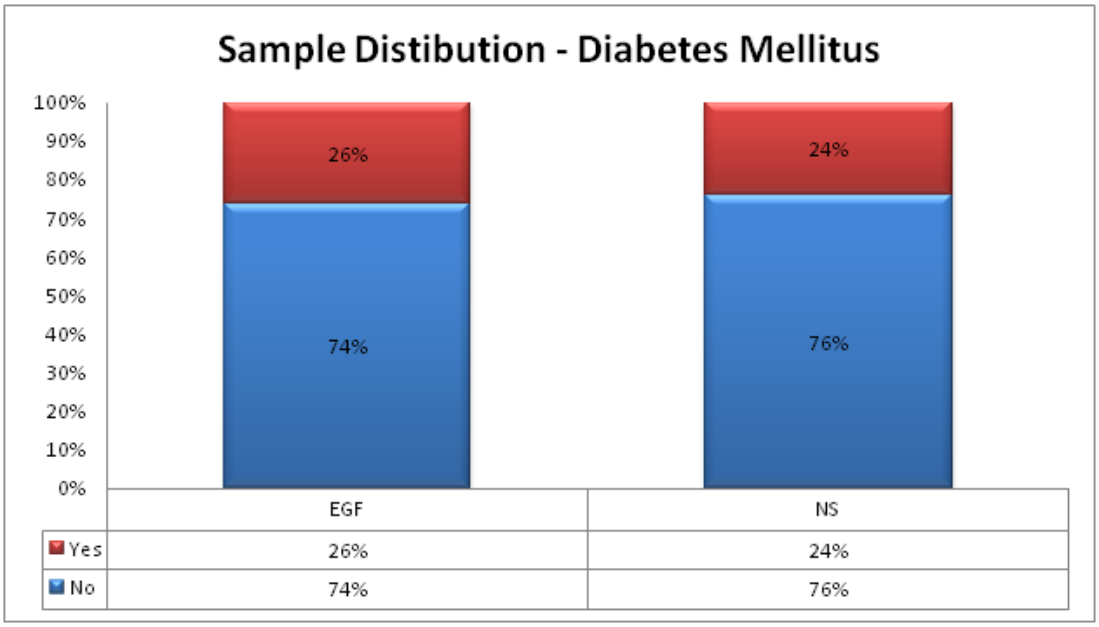
SITE OF ULCERS



Category	Leg	Thigh	Foot	Forearm	Total
EGF	33	7	6	4	50
NS	39	5	1	5	50
Total	**72**	**12**	**7**	**9**	**100**

The most common site of ulcers was the leg which was similar in both groups. The thigh and the foot were the next common. Unusual sites such as forearm, scrotum and back were also present and were equally distributed in both groups.

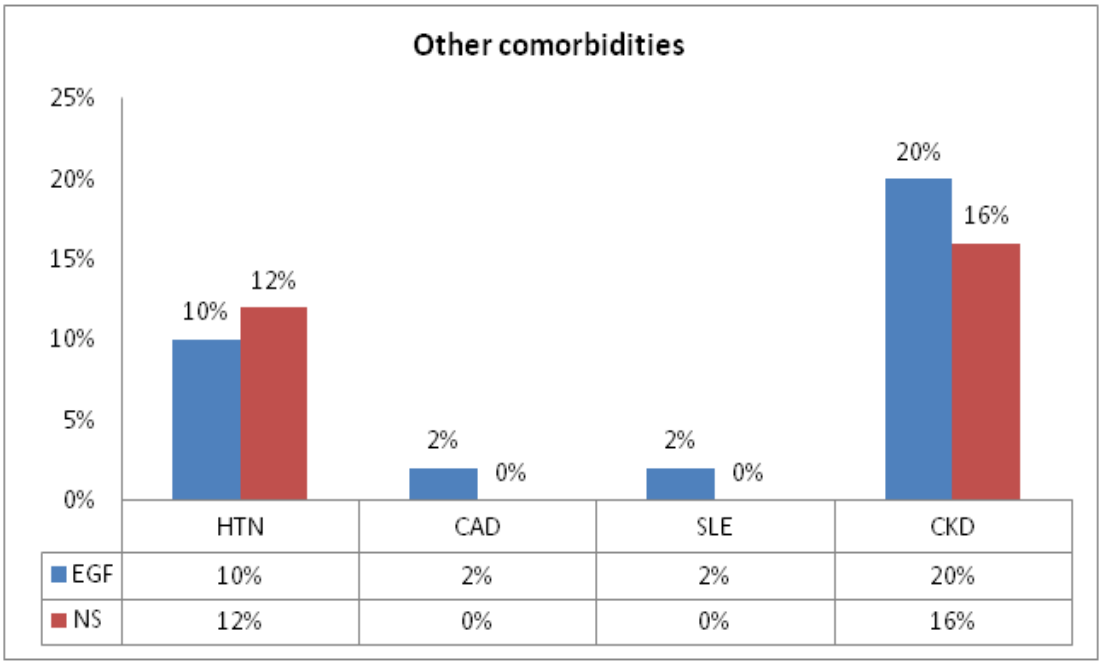
DIABETES MELLITUS



Diabetes	Yes	No	Total
EGF	13	37	50
NS	12	38	50
Total	**25**	**75**	**100**

As we know that DM is the most common etiology of infective ulcers its distribution was plotted and found to be equal in both groups with 75% of the total studied patients being diabetics.

OTHER COMORBIDITIES

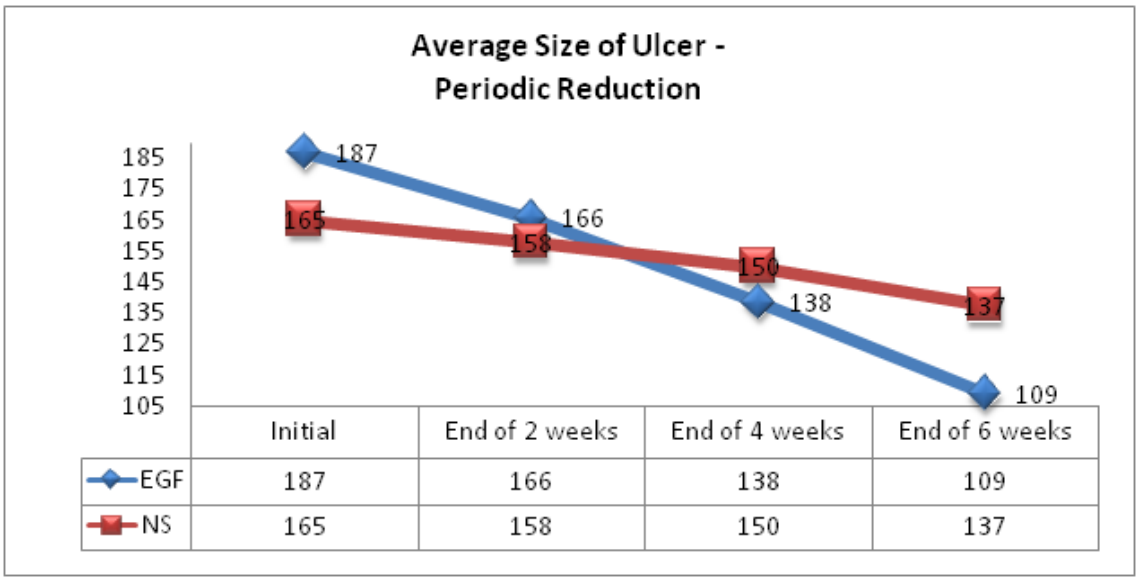


Category	HTN	CAD	SLE	CKD
EGF	5	1	1	10
NS	6	0	0	8
Total	**10**	**1**	**1**	**18**

Other than DM, hypertension, CKD, and CAD were found in both the groups in equal distribution. Identifying these illnesses was important ,as the treatment for these conditions were started and continued along with the ulcer management to avoid bias.

ULCER SIZE

The surface area of the ulcer as measured and recorded at the end of 2nd week, 4th week and 6th week were taken into accountand their mean obtained and plotted as below.



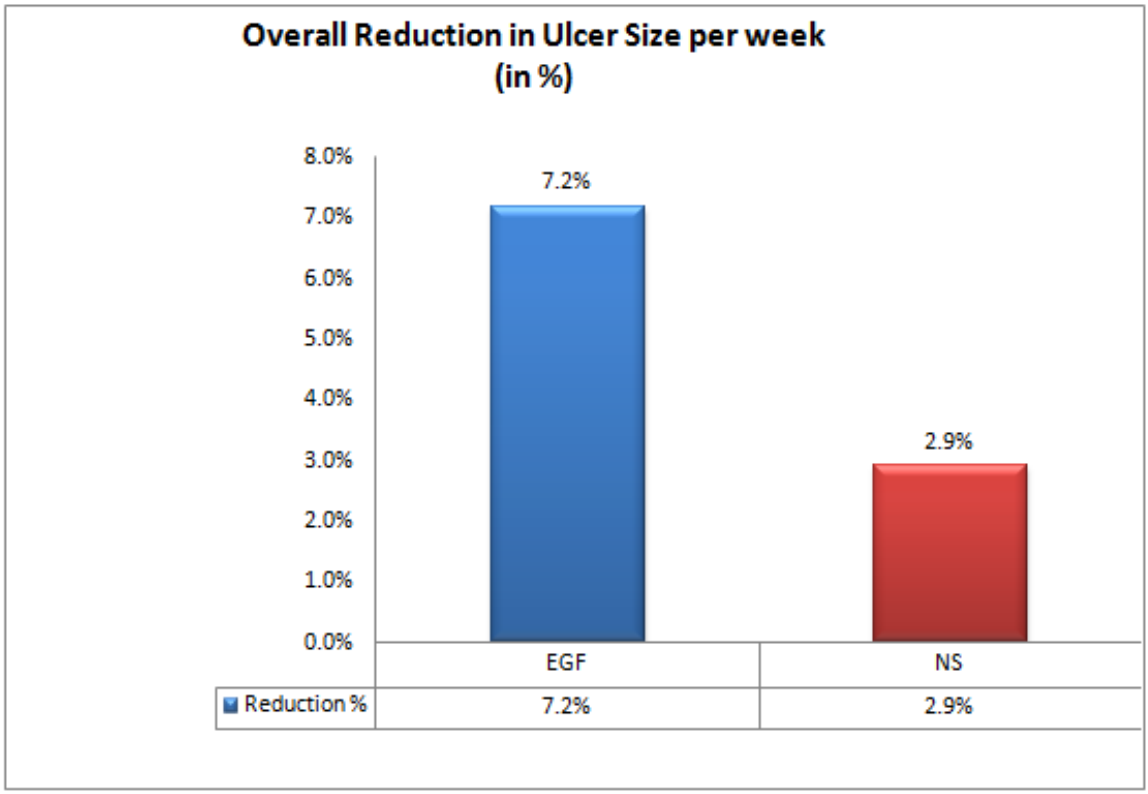
Average Size of Ulcer	Initial	End of 2 weeks	End of 4 weeks	End of 6 weeks
EGF	187	166	138	109
NS	165	158	150	137

The minimum size of ulcer was 86 sq.cm

The maximum size was 284 sq.cm

Mean size being 186.2 sq.cm in study group and 165.06 sq.cm in the control group

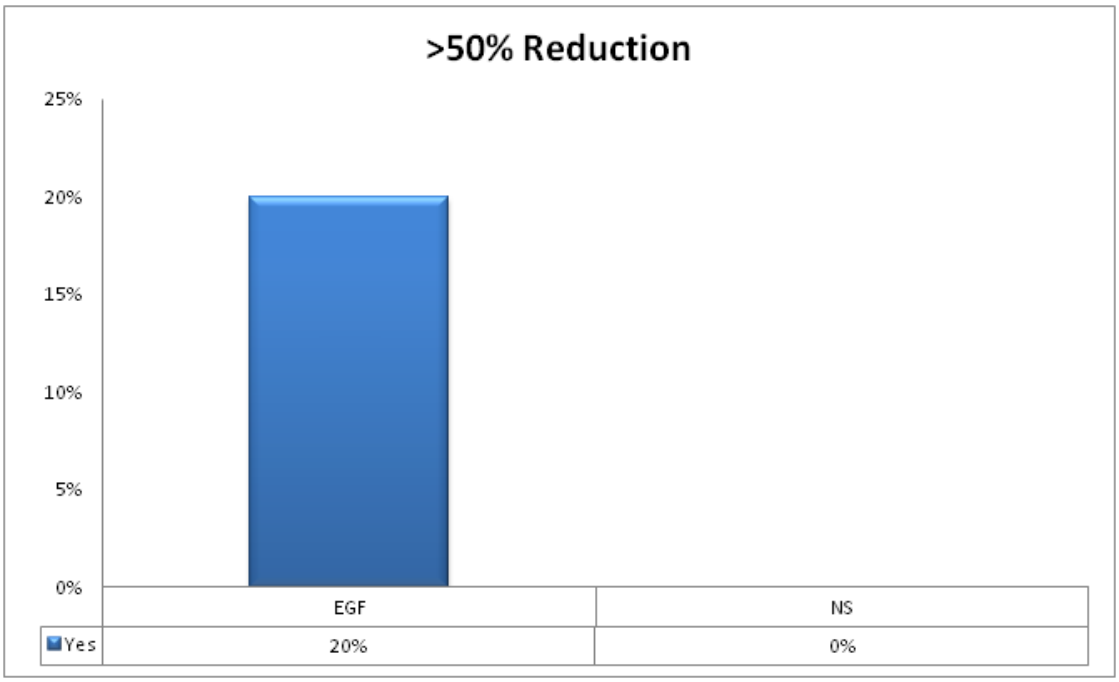
REDUCTION IN ULCER SIZE PER WEEK



Category	Overall Reduction in %
EGF	7.2%
NS	2.9%

The healing rate of study and control groups were analysed by calculating the percentage reduction in size per week in each group. This value was significantly high in the study group at a rate of 7.2% against 2.9% in control group. P value <0.001.

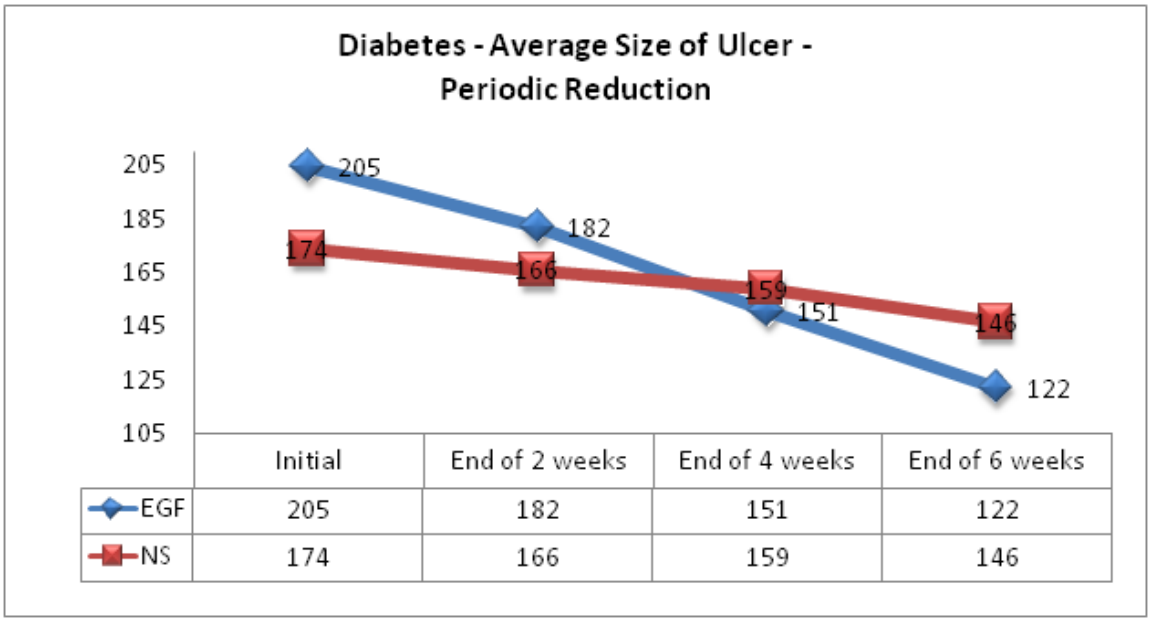
REDUCTION IN SIZE AT 6 WEEKS



>50% Reduction	No	Yes	Total
EGF	40	10	50
NS	50	0	50
Total	**90**	**10**	**100**

Ulcers showing >50% reduction in size at the end of 6 weeks were recorded and analysed and was found to be significantly present in 20% of the study group population. Whereas none of the control group patients showed a 50% reduction in size. P value was <0.001

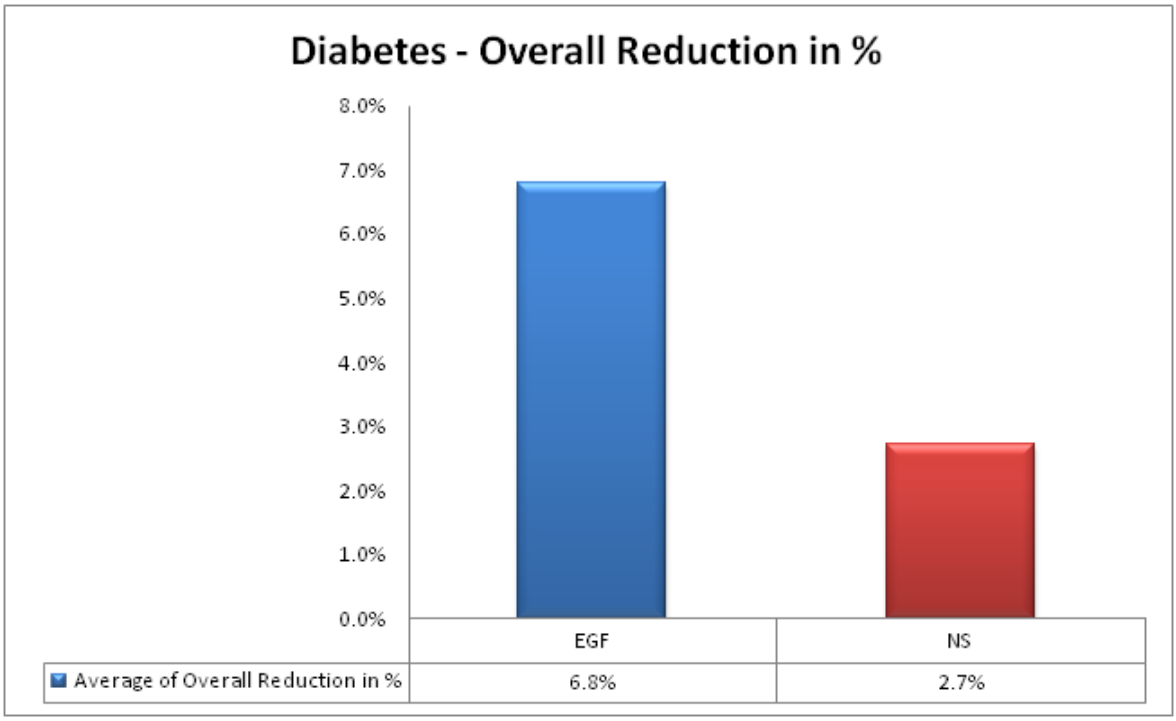
REDUCTION OF SIZE IN DIABETICS



Average Size of Ulcer	Initial	End of 2 weeks	End of 4 weeks	End of 6 weeks
EGF	**205**	**182**	**151**	**122**
NS	**174**	**166**	**159**	**146**

As the entire group comprised predominantly of patients suffering from Diabetes Mellitus the variation that the studied drug could produce on diabetic population were analysed. The size of the ulcer reduced in the study group significantly from a mean of 205 sqcm to 122 sq.cm

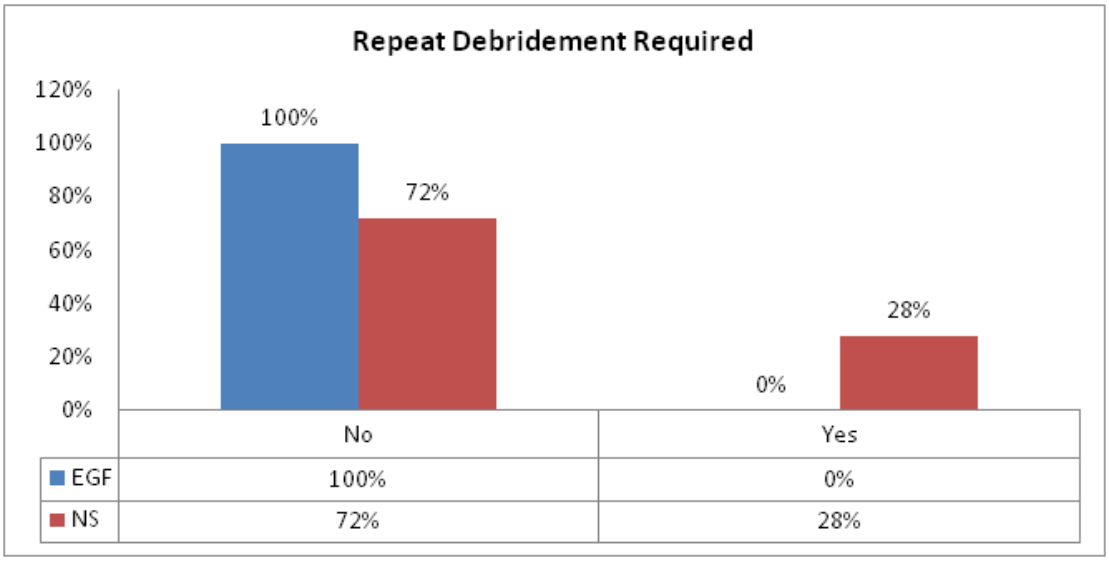
REDUCTION % IN DIABETICS



Category	Average of Overall Reduction in %
EGF	6.8%
NS	2.7%

There was a 6.8% reduction in size per week in the diabetic patients of the study group compared to 2.7% reduction per week in control group.

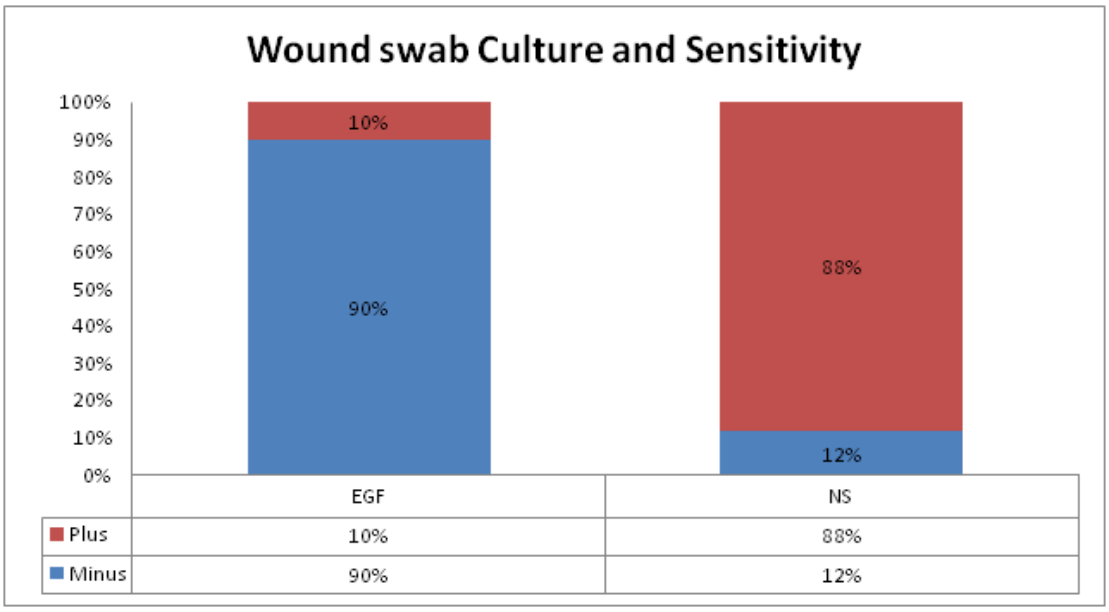
REPEAT DEBRIDEMENT



Category	No	Yes	Total
EGF	50	0	50
NS	36	14	50
Total	**86**	**14**	**100**

None of the patients in study group required repeat debridement. While 28% of the control group patients required debridement during the course of the study. Surgical debridement was done when and where necessary.

WOUND SWAB AT THE END OF 6 WEEKS



Category	Minus	Plus	Total
EGF	45	5	50
NS	6	44	50
Total	**51**	**49**	**100**

The study group surprisingly showed a significant absence of micro organism overgrowth when studied at the end. 90% of the study group had a negative culture compared to the 88% of the control group showing positivity. The p value was <0.001

DISCUSSION

DISCUSSION

Ulcers are being treated with different modalities on a day to day basis at various parts of our country. India being the diabetic capital of the world, have significant number of patients with ulcers that are non-healing adding to the morbidity. The study included all such patients with large or non-healing ulcers.

Age and Sex Distribution:

The mean age in our study was 51.01years in par with the mean age of 51.2 years in the control group. This correlates with other similar studies that have reported a mean age of 52 years. When the ulcers are large or occurring in diabetics the amputation rate is usually higher. Recurrence of ulcers at a same or different site can also occur especially in diabetics.

In our study the ulcers were seen most commonly in males compared to females. The increased incidence in males may be because they are exposed to external environment more when compared to females which is prevalant in the rural part of our country . Further , traumatic ulcers are more common in males owing to the increasing rate of road traffic accidents.

Etiology of ulcers

The most common etiology of ulcers being diabetes mellitus. Which again can be due to one among the following risk factors such as peripheral neuropathy, micro or macro angiopathy, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, impaired visual acuity. The second most common etiology were traumatic either major or minor which get secondary infection. Nonhealing wounds can become stuck in the inflammatory phase of healing, increasing cytokine response with subsequent elevated protease levels and impaired growth factor activity. The study group had major number of diabetics and so the most common etiology was infection followed by trauma. Venous ulcers were only a minor percentage in both groups.

Systemic Disease

Other than hyperglycemia comorbidities such as hypertension, coronary artery disease, chronic kidney disease were present in the sample. Systemic diseases such as cerebro vascular accidents, angina, valvular heart diseases, hypercholesterolemia though prevalent in our country , were not present in the studied group. Because diabetes itself being a multi organ disease all other comorbidities affecting wound healing had to be assessed and managed by a multidisciplinary team for optimal outcomes in ulcer management. That is why we have treated all

our cases with comorbidities with systematic consultation obtained from vascular surgeons, cardiologists, nephrologists, and general physicians. One of our study group patient was sufferring from SLE and the condition was treated concordantly with our ulcer management with periodic review by rheumatologists.

Reduction in ulcer size

In our study there was a significant reduction in size of ulcer in the study group as compared to the control group. Regen D dressing was faster and better in healing ulcers. The mean ulcer size reduced from 187 sq.cm to 109 sq.cm in the regen D group. Whereas the normal saline dressing showed a marginal reduction from 165 sq.cm to 137 sq.cm.

The rate of reduction in size was 7.2% per week in the study group which was much higher than the 2.9% reduction in size in the control group in a week.

The diabetic patients showed an approximately equal reduction rate of 6.8% per week which was again higher than the control group value of 2.7%. Henceforth, diabetes is not found to alter or reduce the efficacy or recombinant EGF in wound healing.

At the end of 6 weeks 20% of patients in the study group showed more than 50% reduction in the size of the ulcer which was a dramatic response when compared to none of the control group patients showing a similar reduction in size.

Repeat debridement

The study group did not require repeat debridement at all as the healthy granulation tissue once appeared in the beginning of second week was floridly covering the entire wound and did not require slough excision until the wound bed was ready for skin grafting. Whereas wounds dressed with normal saline required repeat debridement and slough excision in 28% of the sample size.

Wound swab cultures

The ulcers were periodically swabbed for micro organism growth from the initial debridement till the end of study. According to the sensitivity reports antibiotics were prescribed and administered. The study group dressed with regen D showed a gradual decline in the growth of micro organisms in wound swabs. This may be owed to the increased amount of healthy granulation tissue formation providing local immunity which itself acts as a barrier to microorganism growth. Mixed cultures

were present in the patients showing positivity. Staphylococcus, klebsialla, and pseudomonas were the most common organism grown.

Healing

Overall, the use of recombinant epidermal growth factor is found to improve the rate of ulcer healing be it in diabetics or others. There were no reported side effects of this gel in the study group. And no such side effects have been reported in the literature.

Recombinant human epidermal growth factor stimulates the proliferation and migration of epithelial cells in human culture systems. rhEGF has been shown to enhance the rate of healing thereby quickly providing a healthy surface over the ulcer . The ulcer healing can further be quickened by skin grafts placed over these healthy vascular sterile ulcers.

The morbidity and prolonged hospital stay required to treat large ulcers can thus be reduced by the use of regen D

It is clear that dressings are the only element in the holistic management of patients with ulcers. In addition to dressing selection, emphasis must be made on good glycemic control,pressure reduction, appropriate antibiotic therapy and skilled debridement.

CONCLUSION

CONCLUSION

The results of this study suggest that, within the clinical setting, as part of a comprehensive wound management program

- Diabetes is a more common etiology for large and non-healing ulcers and occurs more commonly over legs
- The Recombinant Human Epidermal Growth Factor is efficient in reducing the size of large ulcers to a significant extent.
- The efficacy of rhEGF does not seem to be lowered in diabetics or other systemic illness.
- The rhEGF is found to significantly lower the infection rate of ulcers.
- rhEGF has an excellent safety profile and easy to use by patients or by care givers outside the clinical setting.
- The use of rhEGF , as indeed of every new therapeutic modality, should not be practised alone, but be incorporated in a holistic strategic approach.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

DATA COLLECTION SHEET

I.Patient particulars:

Name	DOA	Case No.
Age	DOS	I.p.No.
Sex	DOD	Address

Occupation:

II.Diagnosis

III.Chief complaints (with duration)

A.Ulcer

B.Discharge

C.Other complaints

PAST HISTORY:

PERSONAL HISTORY:

EXAMINATION:

INVESTIGATIONS:

MANAGEMENT:

Operated /Non operated-

COURSE DURING STUDY:

ULCER SIZE

on Admission	2 Weeks	4 Weeks	6 Weeks

COMORBIDITIES

ETIOLOGY

SITE OF ULCER

WOUND SWAB C/S

On Admission	2 Weeks	4 Weeks	6 Weeks

REPEAT DEBRIDEMENT

FOLLOW UP:

MASTER CHART

S.No.	Control	Name	Age	Sex	DM	Etiology	Site of ulcer	Size of Ulcer	2 week	4 week	6 week	Overall	>50%	Healthy	Repeat	Wound	Other
1	EGF	Murugan	55	Male	+	infective	Leg	254	230	198	169	5.6%	No	+	-	+	CKD
2	EGF	Kannadasan	49	Male	+	infective	Leg	216	194	160	128	6.8%	No	+	-	+	
3	EGF	Kullan	65	Male	+	infective	Thigh	188	162	134	105	7.4%	No	+	-	-	
4	EGF	Mani	56	Male	+	infective	Leg	164	144	112	85	8.0%	No	+	-	-	CKD
5	EGF	Parvathy	50	Female	-	infective	Thigh	140	118	92	64	9.0%	Yes	+	-	-	
6	EGF	Gunasekaran	45	Male	+	Infective	Leg	240	215	188	155	5.9%	No	+	-	+	HTN
7	EGF	Nambi	68	Male	+	Infective	Leg	221	190	162	134	6.6%	No	+	-	-	CKD
8	EGF	Vanangamudi	65	Male	-	Infective	Gluteal	156	134	98	77	8.4%	Yes	+	-	-	
9	EGF	Hariharan	44	Male	+	Infective	Leg	230	203	176	140	6.5%	No	+	-	-	CKD
10	EGF	Sekar	50	Male	+	Infective	Leg	172	150	123	92	7.8%	No	+	-	-	
11	EGF	Ponraj	32	Male	-	traumatic	Leg	149	129	104	75	8.3%	No	+	-	-	
12	EGF	Vanaja	43	Female	+	Infective	Leg	270	239	202	176	5.8%	No	+	-	-	CKD
13	EGF	Goppu	50	Male	+	Infective	Leg	202	180	154	124	6.4%	No	+	-	-	CKD
14	EGF	Sigamani	55	Male	+	Infective	Leg	182	160	128	99	7.6%	No	+	-	-	
15	EGF	Raja	40	Male	+	Infective	Leg	246	218	181	149	6.6%	No	+	-	-	
16	EGF	Savithri	58	Female	-	traumatic	Foot	98	79	60	43	9.4%	Yes	+	-	-	
17	EGF	Karuna	51	Male	+	Infective	Leg	198	179	153	124	6.2%	No	+	-	-	HTN
18	EGF	Palani	48	Male	+	Infective	Thigh	186	164	139	102	7.5%	No	+	-	-	
19	EGF	Loganathan	50	Male	+	Infective	Leg	158	135	108	79	8.3%	Yes	+	-	-	
20	EGF	Ravichandran	42	Male	+	Infective	Leg	284	246	198	135	8.7%	Yes	+	-	-	HTN,CAD
21	EGF	Mani	45	Male	+	Infective	Thigh	198	177	152	127	6.0%	No	+	-	-	
22	EGF	Gowri	40	Female	-	traumatic	Forearm	102	84	66	42	9.8%	Yes	+	-	-	
23	EGF	Kalyani	70	Female	+	Infective	Leg	235	210	185	157	5.5%	No	+	-	-	CKD
24	EGF	Durai	40	Male	+	venous	Leg	216	192	164	133	6.4%	No	+	-	-	
25	EGF	Asaikannu	65	Female	+	Infective	Foot	114	100	80	55	8.6%	Yes	+	-	-	
26	EGF	Swaminathan	60	Male	+	Infective	Thigh	184	170	139	100	7.6%	No	+	-	-	
27	EGF	Vinayagam	55	Male	+	Infective	Leg	226	202	179	148	5.8%	No	+	-	-	
28	EGF	Murugesan	52	Male	-	Infective	Foot	153	135	110	81	7.8%	No	+	-	-	HTN
29	EGF	Thirupathi	48	Male	+	Infective	Leg	208	185	160	131	6.2%	No	+	-	-	
30	EGF	Senthil	44	Male	+	Infective	Leg	217	195	160	125	7.1%	No	+	-	-	
31	EGF	Pandi	56	Male	-	traumatic	Leg	190	169	142	105	7.5%	No	+	-	-	
32	EGF	Francis	60	Male	+	Infective	Leg	264	240	108	174	5.7%	No	+	-	-	CKD
33	EGF	Inbaraj	38	Male	-	Infective	Foot	86	72	56	38	9.3%	Yes	+	-	-	

34	EGF	Kannan	51	Male	-	Infective	Scrotum	110	95	78	56	8.2%	No	+	-	-	
35	EGF	Sivapriya	34	Female	-	Infective	Gluteal	164	148	125	103	6.2%	No	+	-	-	SLE
36	EGF	Govindan	65	Male	+	Infective	Leg	221	201	174	143	5.9%	No	+	-	-	
37	EGF	Anandan	55	Male	+	Infective	Leg	200	178	153	121	6.6%	No	+	-	-	CKD
38	EGF	Sivakami	68	Female	+	Infective	Leg	175	158	134	99	7.2%	No	+	-	-	
39	EGF	Pradeep	28	Male	+	Infective	Leg	256	222	178	132	8.1%	No	+	-	-	
40	EGF	Muthu	48	Male	-	Infective	Thigh	184	162	136	118	6.0%	No	+	-	+	
41	EGF	Siluvai	67	Male	+	Infective	Leg	182	161	130	100	7.5%	No	+	-	-	HTN
42	EGF	Bhavani	43	Female	+	Infective	Foot	96	84	67	47	8.5%	Yes	+	-	-	
43	EGF	Elumalai	41	Male	+	Infective	Leg	206	181	154	126	6.5%	No	+	-	-	
44	EGF	Bhaskaran	45	Male	+	Infective	Leg	194	179	158	135	5.1%	No	+	-	+	
45	EGF	Hameed	65	Male	+	Infective	Leg	230	206	179	150	5.8%	No	+	-	-	CKD
46	EGF	Raman	50	Male	-	Infective	Foot	121	108	188	56	9.0%	Yes	+	-	-	
47	EGF	Narayanan	48	Male	+	Infective	Leg	168	152	129	102	6.5%	No	+	-	-	
48	EGF	Thiagarajan	47	Male	-	Infective	Thigh	116	107	81	60	8.0%	No	+	-	-	
49	EGF	Durai	45	Male	+	Infective	Leg	159	142	116	88	7.4%	No	+	-	-	
50	EGF	Rajalakshmi	62	Female	+	Infective	Leg	212	199	172	140	5.7%	No	+	-	-	
51	NS	Sivanandi	71	Male	+	infective	Thigh	156	149	140	130	2.8%	No	-	+	+	
52	NS	Ansari	65	Male	+	infective	Leg	126	121	112	100	3.4%	No	-	-	+	
53	NS	Muthu	50	Male	+	Venous	Leg	204	196	182	167	3.0%	No	-	-	+	CKD
54	NS	Kanniappan	54	Male	+	infective	Leg	174	168	160	148	2.5%	No	-	+	+	
55	NS	Packiyam	66	Female	+	Infective	Leg	224	119	202	199	1.9%	No	-	+	+	HTN
56	NS	Eswaran	54	Male	+	Infective	Leg	144	141	135	122	2.5%	No	-	+	+	CKD
57	NS	Punithavathy	55	Female	-	Infective	Thigh	134	128	118	105	3.6%	No	-	-	+	
58	NS	Murugan	48	Male	+	Infective	Leg	168	163	152	140	2.8%	No	-	-	+	CKD
59	NS	Shankar	50	Male	+	Infective	Leg	186	180	170	158	2.5%	No	-	+	+	
60	NS	Leelavathy	46	Female	+	Infective	Leg	126	122	114	102	3.2%	No	-	-	+	CKD
61	NS	Ranganathan	57	Male	+	Infective	Leg	186	179	168	154	2.9%	No	-	-	+	HTN
62	NS	Parameswaran	58	Male	-	Infective	Leg	145	139	118	116	3.3%	No	-	+	+	
63	NS	Kannabiran	71	Male	-	Infective	Leg	194	189	178	165	2.5%	No	-	+	+	
64	NS	Mathialagan	44	Male	+	Infective	Leg	165	158	150	135	3.0%	No	-	-	+	
65	NS	Guruvalappan	45	Male	+	Infective	Back	118	114	106	94	3.4%	No	-	-	+	CKD
66	NS	Vaitheeswaran	50	Male	+	Infective	Leg	204	199	187	172	2.6%	No	-	-	+	HTN
67	NS	Sivamani	68	Male	+	Infective	Thigh	146	138	129	118	3.2%	No	-	-	+	

68	NS	Chandrasekar	60	Male	-	venous	Leg	135	131	120	107	3.5%	No	-	-	-	
69	NS	Shantha	48	Female	+	Infective	Leg	160	155	145	130	3.1%	No	-	-	+	
70	NS	Krishnan	47	Male	+	Infective	Leg	226	218	207	189	2.7%	No	-	+	+	
71	NS	Shankar	38	Male	+	Infective	Leg	154	152	142	128	2.8%	No	-	-	+	
72	NS	Murali	49	Male	+	Infective	Leg	148	141	132	116	3.6%	No	-	-	+	
73	NS	Gopi	54	Male	+	Infective	Leg	186	179	170	158	2.5%	No	-	-	+	CKD
74	NS	Saravanan	45	Male	+	Infective	Leg	235	230	217	202	2.3%	No	-	+	+	
75	NS	Ravichandran	42	Male	+	Infective	Leg	214	211	201	188	2.0%	No	-	+	+	
76	NS	Kalyani	65	Female	+	Infective	Leg	156	154	143	130	2.8%	No	-	-	+	HTN
77	NS	Prabavathy	51	Female	+	Infective	Thigh	134	132	123	111	2.9%	No	-	-	+	
78	NS	Karunanidhi	58	Male	+	Infective	Leg	175	170	160	149	2.5%	No	-	-	+	
79	NS	Appu	45	Male	-	Infective	Gluteal	116	114	106	92	3.4%	No	+	-	-	
80	NS	Duraisamy	60	Male	+	Infective	Leg	239	234	226	219	1.4%	No	-	+	+	CKD
81	NS	Raghu	40	Male	-	traumatic	Scrotum	90	87	79	67	4.3%	No	+	-	-	
82	NS	Durai	52	Male	-	Infective	Leg	142	136	125	111	3.6%	No	-	-	+	
83	NS	Velmurugan	44	Male	+	Infective	Leg	165	165	153	135	3.0%	No	-	-	+	
84	NS	Gowri	48	Female	+	Infective	Leg	246	240	233	222	1.6%	No	-	+	+	CKD
85	NS	Kasiammal	48	Female	+	Infective	Thigh	126	124	112	100	3.4%	No	-	-	-	
86	NS	Rajasekhar	46	Male	+	Infective	Leg	164	158	151	140	2.4%	No	-	-	+	
87	NS	Kanagavel	51	Male	+	Infective	Leg	171	166	154	141	2.9%	No	-	-	+	
88	NS	Ahmed	45	Male	-	Infective	Leg	130	128	118	105	3.2%	No	-	-	+	
89	NS	Veerapandian	48	Male	+	Infective	Leg	196	190	179	164	2.7%	No	-	-	+	
90	NS	Logammal	52	Female	-	Infective	Leg	145	138	129	117	3.2%	No	-	-	+	HTN
91	NS	Dhanasekar	34	Male	-	Infective	Leg	216	201	185	164	4.0%	No	+	-	-	
92	NS	Elumalai	54	Male	+	Infective	Forearm	118	112	106	98	2.8%	No	-	-	+	
93	NS	Sooran	46	Male	+	Infective	Leg	188	181	172	159	2.6%	No	-	-	+	
94	NS	Venkatesan	58	Male	+	Infective	Leg	209	204	196	186	1.8%	No	-	+	+	
95	NS	Gunasekar	50	Male	+	Infective	Leg	228	226	216	206	1.6%	No	-	+	+	
96	NS	Mallika	50	Female	+	Infective	Leg	125	122	114	100	3.3%	No	-	-	+	HTN
97	NS	Dhayalan	56	Male	+	Infective	Leg	176	169	160	146	2.8%	No	-	-	+	
98	NS	Ponni	43	Female	-	Infective	Foot	118	115	106	93	3.5%	No	-	-	+	
99	NS	Ravi	50	Male	+	Infective	Leg	136	128	119	109	3.3%	No	-	-	+	
100	NS	Sathish	30	Male	-	traumatic	Back	86	82	75	66	3.9%	No	+	-	-	